Send Orders for Reprints to reprints@benthamscience.net

Current Medicinal Chemistry, **2020**, *27*, **1-38**

REVIEW ARTICLE

Antidepressants and Antipsychotic Agents as Repurposable Oncological Drug Candidates

Michał Antoszczak[1], Anna Markowska[2], Janina Markowska[3] and Adam Huczyński[1,*]

[1]*Department of Medical Chemistry, Faculty of Chemistry, Adam Mickiewicz University, Poznań, Poland;* [2]*Department of Perinatology and Women's Diseases, Poznań University of Medical Sciences, Poznań, Poland;* [3]*Department of Oncology, Poznań University of Medical Sciences, Poznań, Poland*

ARTICLE HISTORY

Received: April 30, 2020
Revised: May 26, 2020
Accepted: June 10, 2020

DOI:
10.2174/0929867327666200907141452

Abstract: Drug repurposing, also known as drug repositioning/reprofiling, is a relatively new strategy for the identification of alternative uses of well-known therapeutics that are outside the scope of their original medical indications. Such an approach might entail a number of advantages compared to standard *de novo* drug development, including less time needed to introduce the drug to the market, and lower costs. The group of compounds that could be considered as promising candidates for repurposing in oncology include the central nervous system drugs, especially selected antidepressant and antipsychotic agents. In this article, we provide an overview of some antidepressants (citalopram, fluoxetine, paroxetine, sertraline) and antipsychotics (chlorpromazine, pimozide, thioridazine, trifluoperazine) that have the potential to be repurposed as novel chemotherapeutics in cancer treatment, as they have been found to exhibit preventive and/or therapeutic action in cancer patients. Nevertheless, although drug repurposing seems to be an attractive strategy to search for oncological drugs, we would like to clearly indicate that it should not replace the search for new lead structures, but only complement *de novo* drug development.

Keywords: Psychiatric agents, drug development, anticancer activity, *in vitro* tests, *in vivo* studies, chemosensitizers.

1. INTRODUCTION

The search for new drugs against cancer is a tedious and time-consuming process that also requires huge financial outlays; it has been found that the median cost of *de novo* developing a single anticancer agent is nearly $650 million, and involves a duration of even 17 years [1, 2]. Unfortunately, such a process is often unsuccessful, with a low probability to pass testing of the drug on healthy volunteers for safety (phase I clinical trials) [3, 4]. Indeed, only ~10 novel drugs for cancer treatment are eventually approved by the Food and Drug Administration (FDA) every year [1,5,6].

As cancer is a major public health problem worldwide, it is of top interest to use the alternative methods/strategies with low costs and high efficiency to search for new oncological drugs. In this context, drug repurposing, also known as drug repositioning or reprofiling, draws great attention and seems to deliver productivity [7-10]. This relatively new trend relies on the concept of re-investigation of drugs already registered in new therapeutic indications; it allows reduction of the time to introduce the drug to the market, and seems to be extremely beneficial from the financial point of view [11-13].

Because the already registered drugs should have ready-made formulations, there are extensive data on their absorption, distribution, metabolism, elimination and toxicity (ADMET), acceptable therapeutic doses and safety information from clinical trials [3,14,15], so the steps related to their determination might be skipped when registering a known drug for therapeutic use different from its original use. Moreover, ideal candidates for drug repurposing seem also to be the

*Address correspondence to this author at the Department of Medical Chemistry, Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61−614 Poznań, Poland;
E-mail: adhucz@amu.edu.pl; Tel.: +48 61 829 1673

0929-8673/20 $65.00+.00 **© 2020 Bentham Science Publishers**

ones that have been unsuccessful in clinical trials for reasons other than their toxicity [16]. Nevertheless, the off-label use of repurposable drug candidates might be strictly connected with some novel side effects that have not been previously observed, and therefore such therapeutics require usually precise validation in new clinical trials [1].

The number of repurposed drugs is growing systematically [17]. For example, thalidomide, identified originally as an anti-emetic drug, has been successfully repurposed and approved for the therapy of leprosy and multiple myeloma [1,3,7,18], while metformin (Glucophage), an antidiabetic drug, is now in a series of clinical trials as an adjunct agent in adjuvant cancer treatment [1,16,19]. Of note, repurposing existing drugs might also offer a faster path to COVID-19 (coronavirus disease 2019) treatment; commonly used antiparasitic drugs, chloroquine and ivermectin, have been recently used to treat the newly emerged coronavirus (SARS-CoV-2) that has spread globally, and has resulted in a serious coronavirus pandemic [20-23].

On the other hand, accumulated evidence has suggested the positive role of antidepressants and antipsychotic agents in both the reduction of depressive symptoms as well as improvement of quality of life in cancer patients [24–28], for example, by the limitation of a series of distressing cancer-related symptoms. In addition, some of them seemed to have great potential for killing cancer cells *in vitro* and *in vivo* [3,7,29,30].

As it is beyond the scope of this review article to fully summarize and discuss the wide range of studies on central nervous system (CNS) drugs that could be repurposed to be used in oncology, only some promising compounds from the group of antidepressants and antipsychotics have been referenced. Moreover, the following sections have been preceded by a paragraph on the history of the development of this class of psychiatric agents, and have been ended with a brief discussion on the possible challenges and limitations that should be thoroughly considered in future research on the use these compounds in direct anticancer therapy.

2. THE HISTORY OF ANTIDEPRESSANTS AND ANTIPSYCHOTIC AGENTS

Actually, there is a wide library of well-known compounds that have been classified as the CNS drugs; those available to patients could be divided according to their action into (i) antipsychotics, (ii) antidepressants, (iii) anticonvulsants, as well as (iv) antiepileptics [3]. As far as both antidepressants and antipsychotic agents are concerned, the history of their synthesis and development is long, and based rather on a series of findings (Fig. **1A**).

2.1. The Development of Antidepressants

The effective therapies towards depressive disorders were practically not known until the 1930s (Fig. **1A**) [31]; anxious and depressed patients were placed in asylums, where they were subjected to very controversial treatment options, including convulsive and electroconvulsive (electroshock) therapies. Fortunately, this situation was dramatically changed when the first antidepressant agents, iproniazid and imipramine, were broadly introduced into the clinical treatment (Fig. **1A**) [32].

Briefly, as part of the program to find novel antitubercular agents, in 1952, the treatment of patients with iproniazid (Fig. **1B**), a synthetic analog of isoniazid, was accidentally found to stimulate the CNS which was linked with some ‘side effects’, like euphoria, improved sleep, increased appetite, as well as psychostimulation [33-35]. After the clinical test was performed in 1958, it was used off-label to treat patients suffering from major depressive disorder (MDD) [33]. Therefore, iproniazid was the first pharmacological treatment agent for depression from the monoamine oxidase inhibitors (MAOIs) group [31]; the other ones include brofaromine and moclobemide [33].

On the other hand, in parallel to the studies of iproniazid, during the search for new and effective therapeutics against schizophrenia, imipramine (G22355) (Fig. **1B**) was chosen as one of the candidates to test in some psychiatric patients [33,36,37] taking into account its promising sedative properties [31]. Although imipramine did not show any antischizophrenic activity, it produced marked improvements in those suffering from severe depression [33]. Of note, imipramine was the first clinically useful drug from tricyclic antidepressants (TCAs) [31], and was approved by the FDA for the treatment of MDD in 1959 (Fig. **1B**) [33]. Thereafter, a large series of other tricyclics, including amitriptyline, desipramine, dothiepin, iprindole, nortriptyline, protriptyline as well as trimipramine, were also introduced. TCAs are one of the most frequently prescribed class of drugs worldwide [38].

In the late 1960s, some reports strongly suggested a key role of serotonin in MDD [39]. At its simplest, the ‘serotonin hypothesis’ or ‘serotonergic theory of depression’ has clearly proposed that reduced activity of serotonin pathways could have a pivotal role in the pathophysiology of depression [40, 41]. Such a discovery was of fundamental importance to the extensive

studies that have been performed around the world to identify selective ligands that would have the ability to inhibit the reuptake of serotonin in serotonin transporters, and therefore would be classified into the new group of specific antidepressants.

As a result, fluoxetine (LY110140) was the first reported compound from the selective serotonin reuptake inhibitors (SSRIs) group, which was approved by the FDA under the trade name of Prozac after a series of clinical studies in 1987 (Fig. **1**) [42, 43]. Of note, Prozac was the most widely used psychotropic drug in history; also it held second place among the most-sold drugs worldwide in 1994 [32]. With respect to other SSRIs, alongside fluoxetine, several of them were also introduced onto the market, such as citalopram, paroxetine, and sertraline (Fig. **1B**) [32,33]. The SSRIs were simultaneously the first class of rationally designed drugs, as they acted specifically on the protein responsible for the serotonin reuptake, known widely as 5-hydroxytryptamine receptors (5-HTs) [32].

To limit the adverse effects of the use of TCAs and SSRIs, in the last decades, some 'atypical' antidepressant agents have been developed and approved by the FDA [44, 45], for example, bupropion from the group of aminoketones [46, 47], duloxetine, milnacipran and venlafaxine belonging to the unique class of compounds called serotonin-norepinephrine reuptake inhibitors (SNRIs) (Fig. **1A**) [33,48], or 'multi-modal' antidepressant agent – vortioxetine [49].

Unfortunately, although the patients with MDD generally respond well to the monoamine-based treatments, there are some subgroups of patients, especially the treatment-resistant ones, which did not respond well to the therapy applied [33]. Therefore, since 2000, the scientists and clinicians have started to introduce the glutamatergic drugs as the new type of treatment option for those specific patients (Fig. **1A**) [33]. In this interesting class of drugs, ketamine (esketamine) seems to be the most promising one; it received fast-track approval from the FDA as a medication (nasal spray) for depression in 2019 (Fig. **1A**) [50, 51].

Ketamine might be considered as one of the most important drugs synthesized in the 20th century due to its clinical and social impact over the years. A series of recent findings from the clinical trials may encourage the search for other novel glutamatergic modulators against MDD and treatment-resistant depression.

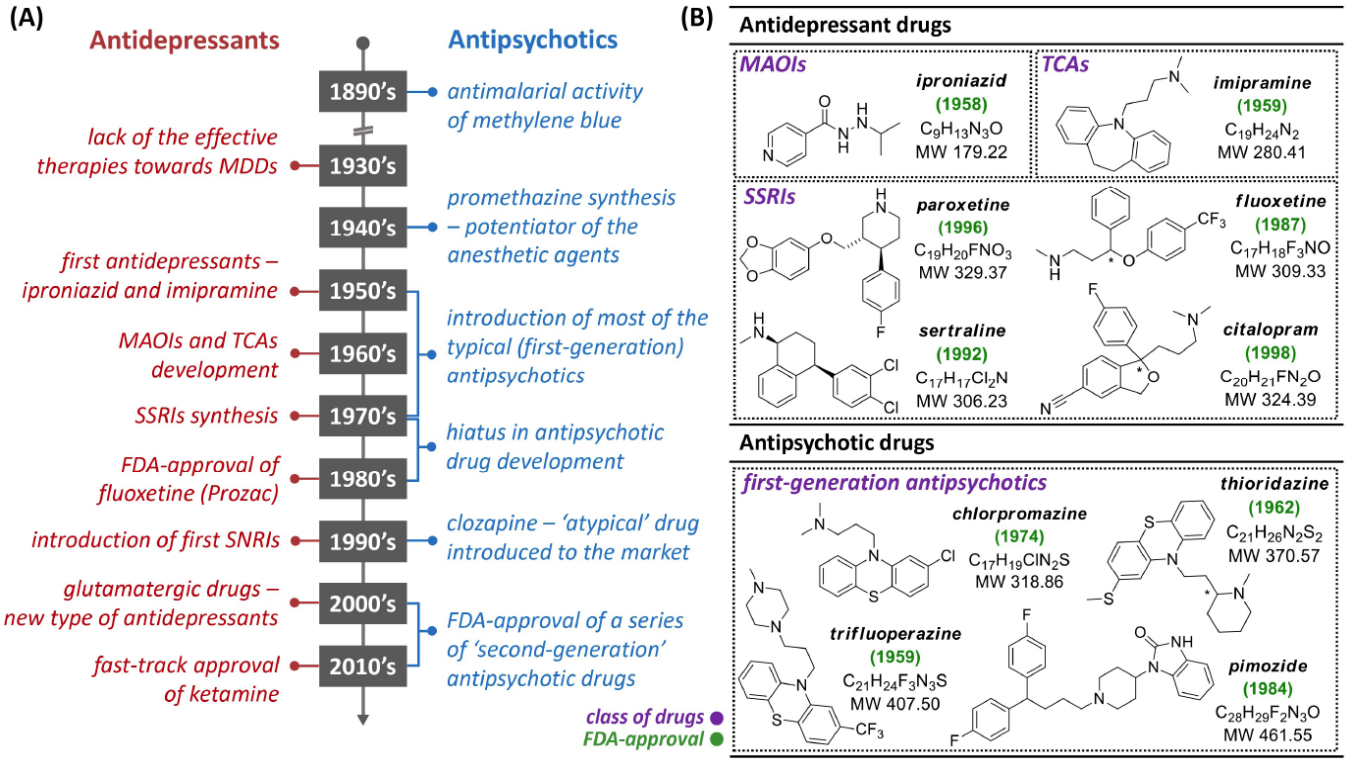

Fig. (1). (A) The milestones of antidepressants and antipsychotics development, and **(B)** the structure and FDA-approval of selected psychiatric drugs. FDA, Food and Drug Administration; MAOIs, monoamine oxidase inhibitors; MDDs, major depressive disorders; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

2.2. The Development of Antipsychotics

In 1876, methylene blue was synthesized for the first time and was further identified for its antimalarial effects by Paul Ehrlich at the end of the 19th century (Fig. **1A**) [52-54]. It encouraged the scientific community to run a series of studies to find other compounds effective in treating the symptoms of malaria. As part of such a program, phenothiazine and a broad library of various aminoalkyl phenothiazines were obtained. Although they did not exhibit antimalarial activity, they were characterized by the antihistaminergic properties [52, 55-57]. In such a group of compounds, promethazine, synthesized firstly in the early 1940s [58], was identified to potentiate the activity of other anesthetic agents (Fig. **1A**), which led to the rapid approval of this drug by the FDA in medical practice [52, 59].

The therapeutic and commercial success of promethazine prompted the researchers around the world to search for other novel phenothiazine derivatives showing activity similar to that exhibited by the native structure. In this context, in 1950, chlorpromazine was synthesized, and was further forwarded for clinical investigation as a possible potentiator of general anesthesia during surgery (Fig. **1**) [58, 60]. Chlorpromazine use has spread very intensively around the world to treat mania, psychomotor excitements, schizophrenia, and also other psychotic disorders [52, 58].

The successful use of chlorpromazine in a series of clinical studies motivated enormous effort and stimulated a widespread search for other antipsychotic drugs with different chemistry, potency, as well as side effect profiles. Most of the typical drugs were introduced between 1954 and 1975, while from 1975 to 1990, there was a hiatus in antipsychotic drug development (Fig. **1A**) [52]. According to some other data, more than 40 drugs, usually referred to as the first-line or first-generation antipsychotics, were introduced around the world by 1990 [61]. This group of compounds included thioridazine, trifluoperazine [62], and pimozide approved by the FDA for the treatment of Tourette's syndrome in 1984 (Fig. **1B**) [63, 64].

In 1954, so just after two years since chlorpromazine was used clinically for the first time, some acute extrapyramidal symptoms (EPSs) were observed and broadly described, such as akathisia, dystonias and pseudoparkinsonism [52, 65], and all of them were connected with the chlorpromazine-based treatment [66]. Thereafter, a large group of clinicians and pharmacologists were convinced of the close relationship between the clinical use of antipsychotics and EPSs [52, 67, 68]. It encouraged the development of the new type of 'atypical' agents which could be characterized by a reduced potential to induce EPSs, an increased efficacy for the positive (delusions, disorganized behavior, and hallucinations), and the negative (affective flattening, apathy, inactivity, poverty of thought, and severe social withdrawal) symptoms of schizophrenia, as well as effectiveness in patients resistant to the commonly used therapeutics [52].

As a result, clinically-confirmed profile with no or low propensity to induce EPSs, and significant efficacy in treatment-resistant patients (both for the positive and negative symptoms) allowed the approval of clozapine [69-74] and its release on the market in the early 1990s (Fig. **1A**) [62]. The success of clozapine-based treatment led to the approval of other 'atypical' agents, known widely as second-generation antipsychotics, that could replace the use of the first-generation counterparts (Fig. **1A**). These agents included asenapine, blonanserin, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone [62], and their introduction has brought great hope of having better pharmacological treatment options for depression available in the near future.

On the other hand, in addition to their original medical indications, some antidepressants and antipsychotics seem to have the potential to be repurposed for the use in oncology not only in the supportive therapy, but also as compounds with significant activity against cancer cells. In the next section, selected repurposable oncological drug candidates from the group of antidepressant and antipsychotic agents have been referenced and discussed. Their main mechanisms of anticancer action and cellular targets have been provided on the basis of the literature data.

3. REPURPOSING OF ANTIDEPRESSANTS AND ANTIPSYCHOTIC AGENTS FOR USE IN ONCOLOGY

Both antidepressants and antipsychotics have been used in clinical therapy for decades, and thus they are well-known agents with strictly defined pharmacokinetic and pharmacodynamic properties. Moreover, some of them have been successfully used for drug repurposing [5].

For instance, many authors have described antidepressants and antipsychotics showing antimicrobial activity, from weak to strong, depending on the drug [75, 76]. This group included thioridazine (Fig. **1B**), which in addition to its antipsychotic effects, was also found to exhibit *in vitro* activity against antibiotic-

sensitive and antibiotic-resistant Gram(+) bacteria, including *Mycobacterium tuberculosis*, methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA, respectively), and vancomycin-resistant *enterococci* (VRE) [77-80]. In addition, several new antidepressant drugs, such as fluoxetine and sertraline (Fig. **1B**), showed antimicrobial effects as well [75, 81]. Although Gram(-) bacteria were found to be generally more resistant to the action of antipsychotic compounds, some of them, like chlorpromazine (Fig. **1B**), showed potent activity towards *Escherichia coli*, *Acinetobacter baumannii* and *Klebsiella pneumonia* [82]. Nevertheless, as the broad spectrum of antimicrobial activities of antidepressants and antipsychotics should not be surprising in view of the proved antidepressant effects of an old tuberculostatic drug – iproniazid (Fig. **1**) [33-35], the additional properties of this class of compounds, including *in vitro* and *in vivo* anticancer effects (Table **1**), could be more unpredictable.

Interestingly, some psychiatric drugs have positive effects on human cancers and are suitable for clinical treatment. Thus, they could be recognized as a generation of promising candidates for chemotherapeutics. Several authors have reported that patients with schizophrenia or other depressive disorders who have been treated with antidepressants or antipsychotic agents have a lower incidence of cancer than those from the untreated general population [5, 83-87]. For example, a lower number of cases of colon, prostate, and rectal cancers has been observed in patients treated with psychiatric drugs [88-90].

Thus, in the next paragraphs, we focused on and discussed the compounds most promising from the group of antidepressants (citalopram, fluoxetine, paroxetine, sertraline) as well as antipsychotics (chlorpromazine, pimozide, thioridazine, trifluoperazine) that have the potential to be repurposed as novel agents in cancer treatment. Firstly, in reference to their original indications, psychiatric drugs may reduce depressive symptoms as well as other psychiatric disorders, especially stress-related and anxiety disorders [91, 92], and thus can improve the quality of life of cancer patients [25-27]. Secondly, equally important, both antidepressants and antipsychotics may be used as adjuvant options to treat non-psychiatric symptoms that are strictly connected with cancer, like fatigue, hot flushes, nausea, pain, pruritus or vomiting [93, 94]. Finally, accumulated evidence has suggested that selected antidepressants and antipsychotic drugs could play an important role in the complementary therapy of cancer [95]. They might inhibit tumor growth indirectly *via* regulating immunity by enhancing cytotoxic activity and/or modulating cytokine production [94], but also directly through inducing the elimination of various cancer cells, both *in vitro* and *in vivo* (Table **1**) [88-90], and by affecting the key cellular mechanisms of carcinogenesis.

3.1. Antidepressant Candidates for Cancer Treatment

3.1.1. Citalopram

Citalopram (Fig. **1B**) is one of the first compounds from the SSRIs group introduced on the market [96] with a specific pharmacodynamic, pharmacokinetic, as well as safety profile [97]; it is well tolerated in the therapeutic dose ranging from 20 to 60 mg per day [98]. Citalopram is used in the treatment of depression, stress-related and anxiety disorders, such as obsessive-compulsive and social anxiety disorders (Table **1**) [24, 96, 98, 99]. Among the SSRIs, citalopram is considered to be the first-line therapy option because it is well-tolerated and poses few drug-drug interactions [24, 100]. Thus, citalopram could be potentially used as an immunoenhancer in chronic pain patients [101], or in psycho-oncology to improve the quality of life of cancer patients. Moreover, as citalopram has a unique chemical structure unrelated to that of other commercially available antidepressants, some additional activities might be expected from this drug that would be outside the scope of its original medical indication. Indeed, citalopram has been identified recently to be a candidate for repurposing to be used in oncology, as it shows cytotoxicity against various types of cancer cells (Table **1**).

3.1.1.1. Colorectal Carcinoma

According to some studies, the use of compounds belonging to the SSRIs group might reduce the risk of colorectal cancer [102-104]. On the basis of the inverse gene expression profiling, the approach to predict new drug candidates that can reduce metastasis in colorectal cancer, citalopram was identified as one of the lead structures [105] because it has a similar profile to those of the well-known antimetastatics, and also shares the same mode of action *via* inhibition of the TGF-β signaling pathway [106]. Importantly, the theoretical calculations were confirmed by experimental results.

The inhibitory effects of citalopram on migration in colorectal cancer cells have been demonstrated both *in vitro* (HCT 116 and HT-29 cancer cell lines) as well as

Table 1. Selected psychiatric drugs with potential anticancer activity.

Compound	Exemplary trade names	Primary indication	Oncological indication	Cancer cell lines	*In vivo* studies	References
Citalopram	Celexa® Cipramil®	Depression Anxiety disorders Stress-related disorders	Acute myeloid leukemia	HL-60		[115, 116]
			Colon cancer and colorectal carcinoma	HCT 116, HT-29	+	[105, 107, 120]
			Hepatocellular carcinoma	HepG2		[110]
			Neuroblastoma	B104, IMR32, Kelly, SH-SY5Y		[113]
Fluoxetine	Adofen® Prozac® Sarafem®	Depression Eating disorders Obsessive-compulsive disorders Panic disorders Premenstrual dysphoric disorders	Burkitt lymphoma	DG-75		[118, 147]
			Breast cancer	Au565, SUM149PT, T47D		[133, 149]
			Cervical cancer	HeLa	+	[152]
			Colon cancer	HT-29	+	[128−130,133]
			Colorectal carcinoma	HCT116	+	[107, 134]
			Glioma and neuroblastoma	C6, SH-SY5Y, SK-N-BE(2)-M17, SKNAS		[133,150, 151]
			Hepatocellular carcinoma	Hep3B	+	[135, 136]
			Lung cancer	A549	+	[133, 136]
			Ovarian cancer	OVCAR-3		[139]
			Prostate cancer	DU-145, LNCaP, PC-3	+	[148]
			Soft tissue sarcoma	TE671		[133]
Paroxetine	Paxil® Seroxat®	Depression Generalized anxiety Obsessive-compulsive disorders Panic attacks Post-traumatic stress disorders Social phobia	Breast cancer	MCF-7		[164]
			Colon cancer and colorectal carcinoma	HCT116, HT-29, LS1034	+	[160, 161]
			Glioma and neuroblastoma	C6, SH-SY5Y		[150]
			Oral cancer	OC2		[165]
			Osteosarcoma	MG63		[166]
			Prostate cancer	22RV1, DU145, LNCaP, PC3		[162, 163]
Sertraline	Zoloft®	Depression Anxiety disorders Eating disorders Premenstrual dysphoric disorders	Breast cancer	MCF-7	+	[182, 183]
			Colon cancer	HT-29, LS1034	+	[160]
			Glioma	C6, U87		[150, 184]
			Hepatocellular carcinoma	HepG2		[171, 174]
			Lung cancer	A549, H522/975, PC9	+	[7]
			Melanoma	A375, B16-F1/F10	+	[186, 187]
			Oral cancer	OC2		[188]

(Table 1) contd….

Compound	Exemplary trade names	Primary indication	Oncological indication	Cancer cell lines	*In vivo* studies	References
			Prostate cancer	PC3		[190]
Chlorpromazine	Largactil® Thorazine®	Schizophrenia psychosis	Breast cancer	MCF-7		[203]
			Colorectal carcinoma	HCT116	+	[29]
			Glioma	C6, U-87MG, U251	+	[197, 199]
			KB carcinoma	KB-ChR-24		[206]
Pimozide	Orap®	Schizophrenia Functional disorders Psychic disorders Tourette's syndrome	Breast cancer	MCF-7, MDA-MB-231/435, T47D, ZR75-1B	+	[214, 219-221]
			Glioblastoma	U87MG		[216]
			Hepatocellular carcinoma	Hep3B/G2, Huh7, MHCC-97L	+	[89, 229]
			Osteosarcoma	U2OS		[230]
			Prostate cancer	22RV1, BHP-1, DU145, LNCaP, PC3/M	+	[227, 228]
Thioridazine	Mellaril® Melleril®	Schizophrenia Other psychoses	Breast cancer	HCC38/1143/1937, MCF-7, MDA-MB-231/435, SUM149/159		[219, 220, 255]
			Cervical and endometrial cancer	C33A, Caski, HEC-1-A, HeLa, KLE		[238]
			Colorectal carcinoma	SW480		[253]
			Gastric cancer	AGS, NCI-N87	+	[254]
			Glioblastoma	GBM8401, U87MG	+	[243, 247]
			Lung cancer	95-D, A549, A549/DDP, NCI-H1299	+	[237, 240, 251]
			Ovarian cancer	A2780, SKOV3, SKOV3/DDP	+	[236, 239-241]
Trifluoperazine	Eskazine® Eskazinyl® Jatroneural® Stelazine®	Schizophrenia Schizophrenia-like illnesses Non-psychotic anxiety	Breast cancer	4T1, BT549, MCF-7, MDA-MB-231/468, SKBR-3, SUM159	+	[268, 269, 272]
			Colorectal carcinoma	HCT116	+	[277]
			Glioblastoma	P3, U87MG, U3005MG, U3028MG, U3046MG	+	[267, 274, 275]
			Hepatocellular carcinoma	Bel-7402, SMMC-7721	+	[278]
			Lung cancer	A549, CL25/97/83/141 and 152, H1975	+	[279]

in vivo, using mouse xenograft tumor model and orthotopic mouse model [105]. According to the obtained data, both the number of circulating tumor cells as well as metastases in distant organs were lower when the mice were treated with citalopram, compared to controls [105].

Such observations were confirmed by other authors; the administration of citalopram reduced colorectal tumor growth in mice, as measured by the changes in tumor volume [107-109]. Although such animal-based preclinical results are not sufficient enough to draw clear, definitive as well as reliable conclusions for human clinical applications, and need further investigation, they seem to be promising, and therefore should encourage more extensive research in this direction.

3.1.1.2. Hepatocellular Carcinoma

In 2017, it was documented that citalopram could exhibit some positive effects towards hepatocellular carcinoma cell line HepG2 by induction of cell death *via* the cytochrome c release as well as the reactive oxygen species (ROS)-dependent activation of the nuclear factor κ-light-chain-enhancer of activated B (NF-κB) [110]. According to the authors of the above paper, citalopram caused also an increase in mitochondrial Bax levels and a decrease in Bcl-2 levels [110]. On the other hand, in the nationwide population-based studies to evaluate the association between the use of well-known antidepressants and risk of hepatocellular carcinoma development, SSRIs, including citalopram, were found to be linked with lower risk of this type of cancer [111, 112]. However, all such findings should be interpreted with caution with respect to the limitations of the obtained data. For example, as mentioned by the authors of these two papers, they could not ensure sufficient accuracy in pathological biopsy diagnosis nor verify the correctness of the doses of the antidepressants used, as well as there was no information on the potential confounding factors among the individuals, such as smoking and lifestyles, which might be also strictly related to the occurrence of hepatocellular carcinoma [111].

3.1.1.3. Neuroblastoma

As the studies on animals are connected with some ethical and practical problems, the *in vitro* tests emerge as a feasible alternative to overcome these limitations. In this context, citalopram has also been assessed recently on a series of rat and human neuroblastoma cell lines, including both non-*MYCN* and *MYCN* amplified ones [113], where *MYCN* is a marker of poor prognosis present in 20% of cancer patients [114]. Of note, citalopram was found to be cytotoxic against non-*MYCN* and *MYCN* amplified cell lines, especially towards IMR32 human cancer cell line [113]. Furthermore, the absence of toxicity in human primary Schwann cells suggested the safety of citalopram for myelin [113]. However, taking the nature of the *in vitro* tests into account, the absence of biokinetics should be mentioned as one of the significant drawbacks of such studies.

3.1.1.4. Other Types of Cancer

In 1999, citalopram at a relatively high micromolar concentration (220 μM) was identified as an agent that has the ability to destroy human acute myeloid leukemia HL-60 cells by the caspase-3-dependent signaling pathway [115], and, similar to its anti-hepatocellular carcinoma mechanism of action [110], *via* the generation of ROS [116]. As the cancer cells function under an exquisite balance of ROS levels, any agents that might increase intracellular ROS disproportionally can induce cell cycle arrest, and finally programmed cell death, known as apoptosis [117]. Because citalopram could increase the intracellular levels of ROS, it may lead to the loss of mitochondrial membrane potential ($\Delta\Psi_m$), caspase activation, and apoptosis in HL-60 cells [115, 116]. Four years later, three structurally distinct SSRIs, including citalopram, were also identified to act directly on cells of Burkitt lymphoma, an aggressive non-Hodgkin B-cell lymphoma, to trigger rapid and extensive programmed cell death [118]. Mechanistically, SSRIs stimulated calcium flux, tyrosine phosphorylation, and down-regulation of the c-Myc and nm23 genes in cancer cells [118]. The apoptosis was preceded by the caspase activation, cleavage of poly-ADP-ribose polymerase 1 (PARP1), DNA fragmentation, the loss of $\Delta\Psi_m$, and the phosphatidylserine (PS) externalization [118].

Cancer treatment usually involves combination therapy with the use of two or more active drugs; in this context, platinum-based therapeutics play a pivotal role as components of such regimens [119]. Interestingly, antidepressants are frequently prescribed concurrently with anticancer drugs, and could exert synergistic, additive or antagonistic effects [120]. In this context, some drug-specific interactions have been observed between citalopram and platinum drugs in cancer treatment; citalopram enhanced cytotoxicity of cisplatin at the early time points in human colon carcinoma HCT116 cells [120]. On the other hand, in combination with citalopram, neither carboplatin nor oxaliplatin exhibited noticeable differences in the effect on these cancer cells [120].

3.1.2. Fluoxetine

Fluoxetine (Fig. **1B**) is a bicyclic antidepressant that is a selective inhibitor of the presynaptic reuptake of serotonin [121]. It has been the first compound approved by the FDA from a group of SSRIs [122, 123]. Fluoxetine (Prozac) was originally introduced into the clinic as the treatment option for patients with depression (Table **1**) [122]. In addition to the therapeutic potential of fluoxetine, the adverse effects of its use were far inferior to those of any other available antidepressants [124]. Thus, Prozac, prescribed to more than 50 million people worldwide, remains the most widely used antidepressant in history; it is currently prescribed not only for depression, but also in the fight against eating disorders, obsessive-compulsive, panic and premenstrual dysphoric disorders (PMDDs) [125]. Because fluoxetine is one of the best known antidepressant drugs, there are also a number of articles and reports in the scientific literature concerned with the properties of this compound that are outside its original medical application; among them is the activity of fluoxetine towards cancer cells (Table **1**).

3.1.2.1. Colon Cancer

The process of growth of new vascular networks, known as angiogenesis, plays a pivotal role in cancer development because it guarantees the adequate supply of oxygen and nutrients that are necessary for the proliferation as well as the metastatic spread of cancer cells [126]. Therefore, any agents that have the ability to target and disrupt the already-formed vessel networks of growing tumors have been actively pursued; the goal of such anticancer therapeutic strategies is to induce a rapid shutdown of the vascular function of the tumor, leading finally to its death [127]. The group of proteins that have been identified as the activators of the process of angiogenesis includes the vascular endothelial growth factor (VEGF) [126]. It should be noted that fluoxetine was found to induce reduction of the expression of VEGF, and to have significant antiproliferative potential against colon cancer cells *in vitro* [128, 129], but also led to reduced microvessel formation as well as tumor shrinkage in xenograft models [130].

Beyond the formation of new blood vessels, characteristic functioning of cancer cells also includes deregulation of the cell cycle and uncontrolled proliferation [94]; the cell cycle is controlled by regulating cyclin-dependent kinases (CDKs) *via* their activator cyclins as well as CDK inhibitors, known as cyclin-dependent kinase inhibitors (CKIs) [131]. Moreover, the p53 protein could play an anticancer role as well, as it might arrest the cell cycle at checkpoints, and thus initiate the programmed cancer cell death [132]. In this context, using the *in vitro* tests, fluoxetine was shown to slow down the cell cycle progression, as well as to inhibit the proliferation of colon HT-29 cancer cells, which are strictly linked with the decreased expression of cyclin A and D1, but also with the increased expression of p21 (CKI-1) and p53 genes [133].

3.1.2.2. Colorectal and Hepatocellular Carcinoma

Fluoxetine has some potential to be used as a potential complimentary agent, offering therapeutic benefits for patients with colorectal and hepatocellular carcinoma. As indicated also for citalopram (Fig. **1B**), using *in vivo* tests, fluoxetine was identified as a drug suppressing the cell division in dimethyl-hydrazine-induced colonic tumors in rats, but also retarding the growth of two rodent models of colorectal carcinomas [107]. In another study, fluoxetine was also shown to selectively induce programmed cell death, and to cause DNA fragmentation in human colorectal cancer cells that seemed to be independent of p53 protein [134]. With respect to hepatocellular carcinoma, fluoxetine induced apoptosis in these cancer cells through the loss of matrix metalloproteinase (MMP), $\Delta\Psi_m$, ROS formation, but also the modulation of mitogen-activated protein kinase (MAPK) activities [135]. The studies of its anticancer mechanism of action also suggested the blockage of the AKT/NF-κB signaling pathway or extracellular signal-related kinases (ERK)/NF-κB activation [136].

However, in contrast to the above referenced article, some other reports suggested that fluoxetine could rather act as an antioxidant agent, leading to reduction of the melanoma-induced oxidative changes in mice spleen [137], as well as lowering the efficiency of superoxide dismutase levels in the brain of hepatoma-bearing mice [138]. Nevertheless, although the studies have brought significant progress in the possible use of fluoxetine for the treatment of colorectal or hepatocellular carcinoma, the precise action of this drug against such cancer cells has not been fully understood yet and requires further investigation.

3.1.2.3. Ovarian Cancer

The fluoxetine-induced apoptotic effects towards human epithelial ovarian cancer cell line (OVCAR-3) were investigated in 2010, in relation to the mitochondria-mediated cell death process as well as NF-κB activation [139]. The results of this study suggested that

fluoxetine could induce the programmed cell death by changing the mitochondrial membrane permeability, leading therefore to cytochrome c release and subsequent activation of caspase-3 [139].

Nevertheless, with respect to ovarian cancer, one aspect strictly connected with fluoxetine, although with other SSRIs as well, should be addressed. Most antidepressant drugs are actively metabolized by the cytochrome P450 (CYP) enzyme system, and therefore a number of drug-drug interactions should be considered as a result of induction/inhibition of such CYP enzymes [140]. Tamoxifen, a hormone therapeutic drug for ovarian cancer [141, 142], is mainly metabolized *via* the CYP2D6 to its much more active form – endoxifen (Fig. **2A**), which is truly responsible for most of the clinical effects [143]. Of note, inhibition of CYP2D6 isoenzyme by some SSRIs, especially by fluoxetine and paroxetine (Fig. **1B**), might hinder anticancer effects of tamoxifen because such agents may decrease the plasma concentration of the active metabolite, leading finally to therapy failure and to increased risk for recurrence of ovarian cancer [144]. Therefore, accumulating evidence has strongly recommended to avoid the use of CYP2D6 inhibitors from the group of SSRIs in cancer patients who are treated with substrates of 2D6, such as tamoxifen, especially in individuals with poor metabolizer phenotype of CYP2D6 [24].

3.1.2.4. Other Types of Cancer

At clinically relevant doses, that is, at concentrations relevant to the treatment of human depression, fluoxetine (~20-80 mg per day) was found to stimulate the growth of cancers in rodent models, such as fibrosarcomas and melanomas [145], while positive response between its usage and breast cancer risk was observed in a case-control study [146]. However, a specific interaction has also been documented with the use of SSRIs in breast cancer patients in combination with selective estrogen receptor modulators (SERM), like tamoxifen [24]. Thus, as tamoxifen could be used against estrogen receptor-positive breast cancer cells [143], every possible negative drug-drug interactions with fluoxetine should be taken into account. Thus, although some evidences support the hypothesized protective effect of the action of fluoxetine on the development of breast cancer, further substantiation from association studies and elucidation of the biological rationale are strongly required.

As far as fluoxetine is concerned, its activity has been specified and extended also to other types of cancer, including Burkitt lymphoma [118] and its drug-resistant variant [147], astrocytoma (a type of brain tumor) [133], lung cancer [133,136], prostate cancer [148], soft tissue sarcomas [133], and breast cancer [133], including its triple-negative variant [149]. From the mechanistic point of view, the observed inhibition of cancer cell proliferation of lung A549 cancer cells might be strictly connected with the inhibition of phosphorylation of ERK1/2, followed by the reduction of phosphorylation of transcription factor c-Myc [133]. Fluoxetine has been proven to induce apoptosis in glioma and neuroblastoma cell lines as well; in this case, the apoptotic changes were preceded by a rapid increase in c-Jun levels, cytochrome c release from mi-

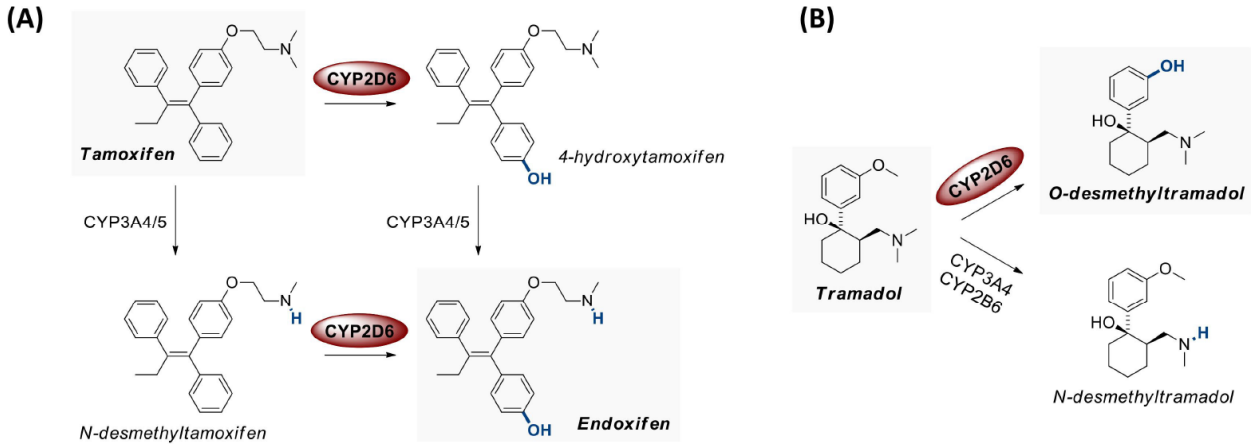

Fig. (2). **(A)** Tamoxifen and **(B)** tramadol metabolized by CYP2D6 to their active metabolites – endoxifen and *O*-desmethyltramadol, respectively. Simultaneous use of these drugs in combination with CYP2D6 inhibitors, such as SSRIs, should be rationally designed, as inappropriate dual therapy may lead to the abolition of the anticancer effects of tamoxifen or the analgesic effect of tramadol. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

tochondria, and increased caspase-3-like activity [150]. The activity of fluoxetine against neuroblastoma cells was further developed by other authors, who showed that this compound induced apoptosis *via* endoplasmic reticulum (ER) stress through the activation of the MAPK signaling pathway as well as histone hyperacetylation [151].

Interestingly, cisplatin-based dual therapy with fluoxetine might significantly inhibit the proliferation of cervical cancer cell line, and could induce cell cycle arrest at G0/G1 phase as well as apoptosis *in vitro* [152]. In addition, fluoxetine and cisplatin combinational therapy might suppress the tumor growth in a HeLa xenograft mouse model in comparison to fluoxetine and cisplatin used alone [153]. Mechanistically, fluoxetine combining with cisplatin might not only suppress the levels of multi-drug resistance (MDR) genes and proteins, such as GST-π and P-glycoproteins (P-gp), but could also affect the levels of genes related to programmed cell death, like down-regulation of Bcl-2, and up-regulation of caspase-9 and p17 [154]. The observation that fluoxetine might be identified as a highly effective chemosensitizer in cancer therapy is very important, as the MDR phenomenon has been responsible for the ineffective treatment of many types of cancer with commonly used cytostatic drugs.

3.1.3. Paroxetine

Paroxetine (Fig. **1B**), another antidepressant belonging to the SSRIs, is the most potent inhibitor of the reuptake of serotonin among the available SSRIs [153] that was approved for clinical use in the 1990s [154, 155]. Clinically, it has been approved as a psychiatric drug for the treatment of depression, generalized anxiety, obsessive-compulsive, as well as post-traumatic stress disorders, but also of social phobia in adults (Table **1**) [153]. In addition, oral paroxetine, at a dose of 10-60 mg per day, is significantly more effective than placebo in reducing the frequency of panic attacks (Table **1**) as well as improving associated symptoms [156]. Although paroxetine is used in therapy of a wider variety of anxiety disorders than any other drug from the antidepressants group [153], its somewhat controversial tolerability profile should always be carefully considered. For example, paroxetine use is strictly connected with cholinergic muscarinic antagonism and potent inhibition of CYP2D6 isoenzyme [157, 158] that should be thoroughly monitored. Nevertheless, paroxetine-based treatment is associated with a much lower rate of adverse events than that of imipramine (Fig. **1B**) and older antidepressant drugs [159]. Probably because of the potential negative consequences of its improper use, there are significantly fewer reports on the anti-cancer activity of paroxetine in the scientific literature, compared for example, to those on citalopram and fluoxetine (Fig. **1B**); however, some interesting data concerning its activity against various types of cancer could also be found (Table **1**).

3.1.3.1. Colon Cancer and Colorectal Carcinoma

In 2008, the effects of paroxetine (and sertraline, Fig. **1B**) on cell viability and proliferation of human colon cancer cell lines HT-29 and the MDR variant LS1034 were evaluated [160]. Both antidepressants induced a dose-dependent inhibition of cell viability and proliferation in both cancer cell lines, with the half maximal inhibitory concentration (IC_{50}) value of 8-15 μM [160]. When compared to the activity of commonly used chemotherapeutics, such as 5-fluorouracil, doxorubicin and vincristine, the SSRIs exhibited comparable activity (HT-29) or a superior effect (LS1034) [160]. From the mechanistic point of view, it has been found that SSRIs arrested cancer cells at the G0/G1 stage and stimulated DNA fragmentation [160]. Both antidepressant agents seemed to induce apoptosis by the caspase-3 activation, an increase in c-Jun levels, and a decrease in the expression of the anti-apoptotic protein Bcl-2; the proapoptotic activity of paroxetine and sertraline might be also accompanied by the MAPK cascade activation [160]. Of note is that using *in vivo* experiments, other authors have recently revealed that the treatment of athymic nude mice bearing HT-29 cancer cells with paroxetine could also remarkably suppress tumor growth [161].

3.1.3.2. Prostate Cancer

Neuroendocrine cells are suggested to be involved in the progression of prostate cancer *via* the secretion of various neuroendocrine products, including serotonin, that have mitogenic effects on adjacent cancer cells, and therefore might contribute to the androgen-independent proliferation of prostate cancer cells [162]. In this context, the effects of paroxetine on the growth and induction of programmed cell death in prostate cancer cell lines were investigated; using *in vitro* tests, paroxetine induced growth inhibition and apoptosis in prostate cancer cells, but the IC_{50} values were in a moderate micromolar concentration range, *i.e.* 21 μM, 30 μM, 36 μM and 39 μM in LNCaP, 22RV1, DU145 and PC3 cancer cells, respectively [162]. In another study, paroxetine was found to increase concentrations of cytosolic-free Ca^{2+} ($[Ca^{2+}]_i$) in PC3 cancer cells at relatively high concentrations (10-150 μM) [163]. According to the authors of the above paper, paroxetine

induced $[Ca^{2+}]_i$ rise by phospholipase C-dependent Ca^{2+} release from the ER, as well as Ca^{2+} influx through store-operated Ca^{2+} channels in a manner regulated by protein kinase C and phospholipase A2 [163]. In both studies, the toxic effects of such therapies to normal cells of the body were, however, unknown.

3.1.3.3. Other Types of Cancer

The association between the use of SSRIs and breast cancer is controversial. However, the effects of SSRIs on some human breast cancer cells have been investigated [164]. Among the five antidepressants tested, paroxetine was found to reduce mostly the viability of MCF-7 and MDA-MB-231 cancer cells in both time- and dose-dependent manner [164]. Mechanistically, the exposure of human breast cancer cells to the action of paroxetine resulted in mitochondrion-mediated programmed cell death, which was also assessed by an increase in the number of cells with sub-G1 DNA content, activation of caspase-8/9, PARP cleavage, and Bax/Bcl-2 ratio, and also by a reduction in $\Delta\Psi_m$ [164]. Furthermore, it was shown that paroxetine increased a generation of ROS, $[Ca^{2+}]_i$, and p38 MAPK activation [164]. Paroxetine also showed a synergistic effect on cell death induced by widely used cytostatic drugs, such as 5-fluorouracil, doxorubicin and taxol, in MCF-7 cells and in a triple-negative variant of breast cancer cells [164].

Potent anticancer properties of paroxetine have been specified and extended also to other types of cancers, including Burkitt lymphoma [118], glioma and neuroblastoma [150], human oral cancer [165], as well as osteosarcoma [166]. The anti-osteosarcoma effect of paroxetine could be connected with the activation of the phosphorylation of ERK, c-Jun *N*-terminal kinase (JNK), and p38 MAPK, but also with the increase in $[Ca^{2+}]_i$ [166].

3.1.4. Sertraline

Sertraline (Fig. **1B**) was among the first compounds from the SSRIs group to be approved for clinical use. It has been available since the beginning of the 1990s [157]. This drug has similar efficacy to other SSRIs in the treatment of depression, including MDD [167], and anxiety disorders; sertraline was also found to be effective against eating disorders and PMDDs (Table **1**) [168]. Importantly, along with other compounds belonging to the SSRIs group, sertraline offers a series of different advantages over older antidepressant agents, such as improved patient tolerability, low risk of lethality in overdose as well as no dependence potential [168]. Sertraline may inhibit CYP2D6 isoenzyme, but to a lesser degree compared to paroxetine (Fig. **1B**), and therefore has a lower likelihood of causing negative drug-drug interactions [169], which is of great value in the subgroups of patients, like the elderly, who usually receive more than one drug regimen [167]. Generally, sertraline has well-established efficacy and favorable safety profile based on decades of clinical use compared to some of the most widely prescribed antidepressant drugs [170]. Of note, potentially novel indications of sertraline for the treatment of various types of cancer have been identified as well (Table **1**).

3.1.4.1. Hepatocellular Carcinoma

The molecular mechanisms of cytotoxicity of sertraline in human hepatocellular cancer cells HepG2 were investigated and characterized in 2014 [171]. Briefly, sertraline was found to significantly activate the intrinsic checkpoint protein caspase-9 as well as cause the release of cytochrome c from mitochondria to cytosol; moreover, this compound markedly increased the expression of tumor necrosis factor (TNF), but also the phosphorylation of JNK, ERK1/2, and p38, suggesting that programmed cell death was induced by it through activation of the TNF-MAP4K4-JNK cascade signaling pathway [171].

High sensitivity of HepG2 cancer cells in the exposure to sertraline was confirmed one year later. In the clinical setting, the plasma concentrations after the administration of sertraline, paroxetine (Fig. **1B**), and duloxetine have been reported to be 0.0992±0.0671 μM, 0.190±0.114 μM, and 0.0704±0.0422 μM, respectively [172, 173], while the order of cytotoxicity in HepG2 cells was sertraline, paroxetine, and duloxetine, with IC_{50} values of 1.24 μM, 7.34 μM, and 8.95 μM, respectively [174]. Therefore, as the plasma concentration of sertraline was about one-half, and nearly equal to that of paroxetine and duloxetine, respectively, this antidepressant agent could have more potent anticancer effects in hepatocellular carcinoma than those of the other antidepressants tested from both the SSRIs and SNRIs groups [174]. Mechanistically, the use of sertraline at relatively low concentration (2 μM) resulted in an increase in caspase-3/7 activity, suggesting that the activation of the caspase signaling pathway might be also be involved in the anticancer effects of this compound towards HepG2 cancer cells [174].

3.1.4.2. Lung Cancer

Both apoptosis as well as autophagy are key mechanisms in mediating cell survival and death [94]. The process of induction of apoptosis results from a cascade

of caspase activation that may be initiated by a series of extrinsic stimulating factors (receptor-mediated) or by intrinsic ones (mitochondrial-mediated) [175]. During the cancer formation, the apoptotic signaling pathway is impaired or perverted, and therefore much effort regarding the search for effective anticancer therapeutic strategies refers to restoring apoptosis [176]. Equally important as apoptosis is also autophagy. This process maintains cellular homeostasis *via* both degrading and recycling damaged intracellular proteins and organelles in lysosomes [94, 176]. Thus, autophagy provides substrates for the generation of energy, but also biosynthesis in stress, and is identified as a 'double-edged sword' that, on one hand, may result in induction of death of cancer cells, and on the other hand can provide cancer cells with nutrients as well as may promote their survival [176].

In this context, as far as anticancer activity of sertraline is concerned, an interesting finding seemed to be that sertraline inhibited the viability of non-small cell lung cancer cells, both *in vitro* and *in vivo*, and showed a synergistic action with a commonly used cytostatic drug – erlotinib; more specifically, a dual therapy with the use of sertraline and erlotinib was found to effectively promote autophagic flux in these cancer cells [7]. The mechanistic studies performed by the authors of the above paper clearly demonstrated that such combined therapy reciprocally regulated the AMP-activated protein kinase (AMPK)/the mechanistic target of rapamycin (mTOR) signaling pathway, while the blockade of AMPK activation was found to decrease the activity of either sertraline used alone or in combination with erlotinib [7]. The peak plasma level of sertraline could reach ~583 nM at the recommended dosage (200 mg per day) [177], that is, at a much lower concentration that was used in the *in vitro* tests. Fortunately, sertraline showed the ability to enrich in lung tissue by even ~39 μM [178-180], so the IC_{50} value of sertraline (15 μM) obtained at cellular levels might be very promising [7]. Anyway, although sertraline as a potentially new anticancer agent against non-small cell lung cancer cells seemed to have good pharmacokinetic profile, further studies are still needed to determine the optimal dosage for its clinical application.

3.1.4.3. Other Types of Cancer

Because of the paradoxical finding on the use of some antidepressant agents in tamoxifen-treated patients, care must be taken when considering the possible benefits towards risks of concurrent use of tamoxifen and antidepressants with potent CYP2D6 inhibition profile (Fig. **2A**) [181]. Thus, pragmatism should strongly suggest preferential avoidance of the antidepressant agents, which are known to strongly inhibit CYP2D6 isoenzyme, and those imparting less inhibition properties, including sertraline [181], in the combination treatment of such types of cancer in which tamoxifen is commonly used, *e.g.* in breast cancer. Intriguingly, sertraline demonstrated antiproliferative activity towards breast cancer cell line MCF-7 through targeting the mTOR signaling pathway [182]. In another study, it was confirmed that sertraline induced apoptosis in MCF-7 breast cancer cells with the IC_{50} of about 16 μM, as evidenced by morphological changes, PS externalization, as well as PARP cleavage [183]. Also sensitive to the action of sertraline are the cancers of colon, including its MDR variant [160], glioma (combination with imatinib) [150,184], T-cell leukemia [185], melanoma [186, 187], oral [188], aggressive form of ovarian (combination with Doxil®, so pegylated liposomal doxorubicin) [189], and prostate [190].

3.2. Antipsychotic Candidates for Cancer Treatment

3.2.1. Chlorpromazine

Chlorpromazine (Fig. **1B**) is an aliphatic phenothiazine analog that is one of the widely-used agents [191] belonging to the first generation antipsychotics [192]. According to the WHO Model Lists of Essential Medicines, chlorpromazine was referenced as one of five therapeutics used in the fight against psychotic disorders [193]. Moreover, it has been used as a 'gold standard' to compare the efficacy of both older and newly developed antipsychotic agents [191]. Of note is that chlorpromazine is an effective and global standard treatment for psychosis, as well as behavioral disturbances in patients with schizophrenia and schizophrenia-like psychoses (Table **1**) [194]; this drug works through blocking 'monoaminergic' receptors, particularly dopamine receptor [195]. Importantly, when monitoring carefully, chlorpromazine is well tolerated by patients [196]. Chlorpromazine was instrumental in the development of a new discipline dedicated to the study of mental pathology with the employment of centrally acting drugs, known as neuropsychopharmacology [60]. The compounds from the group of phenothiazines, such as chlorpromazine, were also found to suppress proliferation and induce apoptosis of a series of cancer cells (Table **1**), thus suggesting the potential of these drugs to be repurposed as novel anticancer agents.

3.2.1.1. Glioma

Noteworthy is that chlorpromazine exhibited the antiproliferative activity towards some brain tumors [197-

198]. Firstly, treatment with chlorpromazine resulted in cell-cycle arrest at the G2/M phase in rat C6 glioma cells through the reduction of the expression of cell cycle-related proteins, including cyclin A, B1 and D1, but also *via* the induction of the increase in the $p21^{Waf1/Cip1}$ level [197]. Secondly, it was also found that chlorpromazine induced autophagic cell death in human U-87MG glioma cells, but no apoptosis of these cancer cells [198]. Mechanistically, chlorpromazine inhibited phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway in U-87MG cells [198]. Of note, when U-87MG cells were implanted into the brain of an athymic nude mouse, chlorpromazine was found to trigger autophagy as well as inhibit xenograft tumor growth [198]. On the other hand, in 2017, it was proved that chlorpromazine selectively inhibited the proliferation of chemoresistant glioma cells, but also glioma stem cells [199]. In this case, chlorpromazine mode of action was based mainly on the inhibition of cytochrome c oxidase (CcO, complex IV) activity from the chemoresistant variant of glioma cells, but not from chemosensitive ones, without affecting other mitochondrial complexes [199].

3.2.1.2. Colorectal Carcinoma

As regarding the effects of the use of chlorpromazine in cancer treatment, it has also been shown that this compound induced tumor apoptosis through a p53-dependent manner, and suppressed xenograft tumor growth in colorectal cancer [29]. The activation of JNK was crucial for chlorpromazine-induced p53 expression, and the subsequent induction of tumor programmed cell death [29]. Further, the induction of p53 acetylation at lysine382 was involved in chlorpromazine-mediated tumor apoptosis; this induction was attenuated by sirtuin 1 (SIRT1), a class III histone deacetylase [29]. Importantly, the inhibitory activity of chlorpromazine showed specificity against tumor cells compared to normal fibroblasts [29]. In addition, chlorpromazine showed low toxicity in both mice and zebrafish embryos, suggesting the therapeutic potential of this compound in the fight towards colorectal carcinoma cells *in vivo* [29]. Further studies are required to confirm not only these promising results, but also the possible interactions between chlorpromazine and other conventional chemotherapeutic drugs.

3.2.1.3. Other Types of Cancer

Scientific literature provides several reports describing the activity of chlorpromazine against other than the above-mentioned types of cancers. With a recent advance in genomics, the Connectivity Map (CMap) database has revealed potential associations between small molecules and various diseases, including the activity of some antipsychotic drugs against cancer cells [16, 200, 201]. Using CMap, cell viability as well as clonogenic assays, 28 compounds were identified to exhibit *in vitro* activity against hepatocellular carcinoma, and two of them, chlorpromazine and trifluoperazine (Fig. **1B**), were further selected for the tests in mice [200]. Interestingly, both antipsychotic drugs inhibited orthotopic liver tumor growth [200].

In a study conducted in 2010, a series of six antipsychotic agents were screened for their effects against various tumor cell lines derived from lymphoblastoma, neuroblastoma, non-small cell lung cancer, as well as breast adenocarcinoma; almost all these drugs, including chlorpromazine, selectively inhibited the growth of cancer cells studied [202]. As far as breast cancer is concerned, a chlorpromazine-based treatment option was found to improve the therapeutic efficacy towards tamoxifen-resistant variant of breast cancer, enhancing the cytotoxic effects of the use of tamoxifen [203]. Moreover, chlorpromazine was identified as an agent that might inhibit the growth of mouse melanoma [204], and murine sarcoma [205].

With respect to the MDR cancer cells, it was shown that chlorpromazine might have the ability to sensitize human KB carcinoma cells to the action of a series of cytostatic drugs, including dactinomycin, daunorubicin, doxorubicin, as well as vinblastine, but only partially to that of colchicine and vincristine [206]. Another interesting finding clearly evidenced that high chlorpromazine concentrations may increase the effectiveness of mitomycin C against Ehrilch ascites tumor (EAT) cells [207]. Furthermore, some studies suggested that the addition of chlorpromazine to anticancer drug blemycin may augment the therapeutic efficacy of bleomycin *in vivo*, without increasing its toxicity [208], while a somewhat controversial combination of chlorpromazine and an antiparasitic agent pentamidine showed synergistic antiproliferative effects *via* dual mitotic action on the growth of tumor cell lines *in vivo* [209]. Such data suggested that chlorpromazine-based treatment within the observed human plasma concentration range should be tested along with other cytostatic agents for their possible synergistic drug-drug interactions to evaluate the therapeutic potential of such combinations in further clinical applications.

3.2.2. Pimozide

Pimozide (Fig. **1B**), an antipsychotic agent that belongs to diphenylbutylpiperadines, is widely used in the

treatment of chronic schizophrenia as well as psychic and functional disorders (Table **1**) [210]. It has been found to be effective in the treatment of the negative symptoms of schizophrenia and other delusional states [211]; pimozide is also FDA-approved for treating Tourette's syndrome [212]. This antipsychotic drug is metabolized mainly by CYP3A4, and its therapeutic action is based on the selective inhibition of dopamine D1/D2 receptors, and additionally, calcium channels [212]. Of note, some studies have also shown that pimozide has anticancer activity in numerous malignancies, such as breast cancer, glioblastoma, hepatocellular carcinoma, osteosarcoma and prostate cancer (Table **1**) [213-217]. The mechanism of the anticancer activity of pimozide includes mainly: (i) inhibition of cell growth and proliferation, and promotion of apoptosis, which then causes cell cycle arrest [214]; (ii) inhibition of angiogenesis by blocking VEGF as well as the AKT signaling pathway, which is associated with the positive effects on tumor progression, and the ability of cancer cells to migrate and invade [214]; (iii) weakening of the function of signal transducers and activators of transcription 3 (STAT3), a member of the family of proteins whose phosphorylation causes proliferative and anti-apoptotic activity, but also supports the renewal of small sub-population of cancer stem cells (CSCs) [213-215, 218]; (iv) blocking of CSCs activity by inhibition of the Wnt/β-catenin signaling pathway [213, 215, 216]; and finally (v) lowering of the expression of MMP, endopeptidases affecting many stages of cancer development, which limits the progression, proliferation, invasiveness and migration of cancer cells, induces programmed cell death, and inhibits the formation of new vessels [214].

3.2.2.1. Breast Cancer

Importantly, *in vitro* studies performed on MCF-7 cell line derived from breast cancer have clearly shown that pimozide might inhibit the proliferation of estradiol-induced cancer cells [219]. In addition, pimozide was found to reduce the growth of two other breast cancer cell lines, *i.e.* tamoxifen-sensitive and tamoxifen-resistant ones (MDA-MB-231 and MDA-MB-435, respectively) [220]. Thus, the authors suggested that pimozide could be active in breast cancer with either positive and negative estrogen receptor, and might be an alternative to tamoxifen-based treatment [220]. Such activity of pimozide consists of anti-antagonistic action on the modulator protein – calmodulin, which acquires the ability to stimulate many enzymes and other proteins due to the attachment of Ca^{2+} cations [220]. A significant reduction in the survival of MCF-7 breast cancer cells was also reported if pimozide (2.5 μM) was added to γ-irradiated cells [221].

According to other studies, the anticancer potential of pimozide could also rely on the eradication of CSCs *via* inhibition of the Wnt/β-catenin signaling pathway, as well as on decreasing the activity of STAT3 [213]. In addition, such eradication takes place through a complicated process associated with the inhibition of the ubiquitin specific peptidase 1 (USP1)/WD complex, regulating DNA repair and overcoming resistance to the action of cytostatics [213]. In another study, pimozide inhibited proliferation and promoted apoptosis in breast cancer cell lines, but also inhibited angiogenesis in xenografts, as well as reduced the number of lung metastases by blocking VEGF receptor 2 (VEGFR2) and inhibiting the AKT signaling pathway; it has been suggested that reduction of AKT signaling pathway might be due to dopamine receptor D2 (DRD2) inhibition [214]. Furthermore, in both the *in vitro* and *in vivo* studies, it has been shown that pimozide reduced the expression and activity of MMP, which inhibited invasion and metastasis, and also reduced the expression of Ras-related nuclear (Ran) protein [214]. Thus, pimozide could be a promising therapeutic option against highly aggressive triple-negative variants as well, which accounts for 15-20% of all breast cancers [214].

3.2.2.2. Glioblastoma

Standard therapies of glioblastoma are ineffective, being associated with both the molecular heterogeneity of glioblastoma multiforme and the resistance of most of these tumors to the therapeutic methods applied; resistance to the treatment is caused by the presence of cancer cells with stem-like phenotype as well as with the inability of temozolomide to cross the blood-brain barrier [222, 223].

Fortunately, strong inhibition of dopamine D2 receptors by pimozide could be associated with a decrease in glioma stem cell activity [216]. The *in vitro* assay with pimozide in the U87 glioblastoma cell line showed an inhibitory effect on the proliferation and invasiveness of these cells, and the result of such effects was a decrease in stem cell markers – Nestin and SOX2 [216]. However, the authors of the above paper suggested that the activity of pimozide towards glioma stem cells might also result from the impact of this agent on other factors, including cell adhesion or modulation of signaling pathways, like epidermal growth factor receptor (EGFR) [216].

Other studies have demonstrated that the key cause of failure of glioblastoma treatment may be the overex-

pression of oncogene – inhibitor of DNA binding 1 (ID1) [224, 225]. Its product, ID1 protein, shows increased activity in many advanced cancer types, which affects cell growth, survival, migration, invasion and angiogenesis, and thus leads to poor prognosis [224, 225]. In addition, it promotes tumor growth by activating the EGF-mediated signaling pathway, and increases resistance to chemotherapy [224, 225]. In this context, the *in vitro* studies on the effect of pimozide on glioblastoma U251 cell line and glioblastoma stem cell lines (G811 and H818), but also the *in vivo* tests on glioma xenografts in mouse brain indicated that this drug revealed extremely beneficial anticancer effects [224]. Pimozide sensitized the glioma cells to radiation-induced death, and if used concomitantly with temozolomide, it delayed relapse and significantly prolonged survival in animals [224]. This beneficial effect of pimozide was most likely due to its permeability across the blood-brain barrier, and the reduction of ID1 expression by interfering with ubiquitination by USP1 [226]; pimozide reduced EGFR signaling pathway as well through inhibition of ID1 activity [224].

3.2.2.3. Other Types of Cancer

Besides the activity against breast cancer and glioblastoma, pimozide was also effective toward other types of cancer. Pimozide inhibited cell growth and cellular STAT3 activation in prostate cancer cells in both dose- and time-dependent manner by inducing G1 phase cell cycle arrest, downregulated the ability of colony formation and sphere-forming, and suppressed cells migration [227]. Recently, the mechanism of the anti-prostate cancer activity of pimozide has been intensively studied. This compound was found to increase the generation of ROS in two cell lines used (DU145 and PC3), and inhibited their proliferation, migration, and colony formation, while administration of pimozide to transgenic mice with prostate cancer reduced the progression of prostate cancer not only with increased ROS generation, but also with decreased superoxide dismutase (SOD) activity [228].

As far as hepatocellular carcinoma is concerned, pimozide has been identified to effectively inhibit cell growth of hepatocellular carcinoma cells through disruption of the Wnt/β-catenin signaling pathway as well as reduction of expression of epithelial cell adhesion molecule (EpCAM), known as a hepatic stem cell marker that is a functional down-stream target of the Wnt/β-catenin signaling pathway [229]. Of note is that pimozide inhibited the maintenance and tumorigenicity of hepatocellular carcinoma stem-like cells, particularly the side population or $CD133^+$ cancer cells, evaluated by colony and sphere formation, as well as transwell migration assays [89]. Similarly, pimozide inhibited cell proliferation, colony and sphere formation capacities of the osteosarcoma cells, inducing G0/G1 phase cell cycle arrest, but also reduced the percentage of a small sub-population of cancer cells with stem-like phenotype [230]. Interestingly, anticancer effects of pimozide in melanoma were significantly enhanced when this agent was combined with indoleamine 2,3-dioxygenase inhibitor – L-MT [231], but this psychiatric drug might act as a potent sensitizing agent as well. For example, pimozide noticeably enhanced the sensitivity of osteosarcoma cells to 5-fluorouracil-induced proliferative inhibition [230].

3.2.3. Thioridazine

Thioridazine (Fig. **1B**) is a piperidine phenothiazine that is used as an antipsychotic drug to treat schizophrenia and other psychoses (Table **1**); it has often been considered the drug of choice in the elderly because of reputed low risk of EPSs [232, 233]. The use of this antipsychotic is reserved for patients who have failed to respond to or cannot tolerate treatment strategies based on other antipsychotic agents [234]. However, thioridazine may cause a series of cognitive adverse events, including delirium or worsening of memory, but also pigmentary retinopathy [233]. Moreover, as thioridazine is actively metabolized by CYP2D6, its co-administration with drugs that inhibit CYP2D6, such as fluoxetine and paroxetine, or with those that have the ability to inhibit the metabolism of thioridazine, including fluvoxamine and pindolol, should be avoided [234]. Numerous studies have shown additionally that thioridazine exhibits the anticancer activity (Table **1**) [88, 235-238], and the pleiotropic mechanism of this action includes (i) inhibition of cancer cell proliferation, resulting from a decrease in the activity of cyclin D/cyclin-dependent kinase 4 (CDK4) complex or the complex of cyclin A with cyclin-dependent kinase 2 (CDK2) [239], stimulation of the activity of p21 and p27 proteins that are known as potent inhibitors of CDK [239], as well as inhibition of PI3K/AKT signaling pathway [88, 238-239]; (ii) induction of apoptosis by activation of caspase 3 and 9 [236, 238, 240], as well as decrease in Bcl-2 antiapoptotic activity and Bax proapoptotic growth [240]; (iii) inhibition of angiogenesis through decrease in the expression of hypoxia-inducible factor 1α (HIF-1α) as well as associated VEGF [236, 241], and suppression of the focal adhesion kinase (FAK)/mTOR signaling pathway [238, 242]; (iv) promotion of autophagy [236, 243]; and (v) inhibition of CSCs survival [237, 244].

3.2.3.1. Glioblastoma

Glioblastoma, also known as glioblastoma multiforme, is one of the most common brain tumors with different histological subtypes diagnosed on the basis of genetic signature analysis [245]. Although some advances in both radio- and chemotherapy, including temozolomide and cisplatin treatment options have been made, the prognosis for this type of tumor is poor; it is strictly connected with its resistance to the action of cytostatics and the presence of anatomical and functional barriers, *i.e.,* blood-brain-barrier [245]. On the other hand, although temozolomide interferes with the synthesis of DNA, RNA, and numerous proteins, and therefore affects cancer cell division, this compound exhibits some side effects on normal, rapidly dividing body tissues, like bone marrow [246].

Using a multicentre study on five human glioblastoma cell lines and an animal model (nude mice), the use of thioridazine in combination with temozolomide has been found to significantly improve the results of glioblastoma multiforme therapy, without significant toxicity [246]. In this case, thioridazine action was to sensitize glioblastoma cells to the action of temozolomide by impairing autophagy [246]. In another study on glioblastoma cell lines, it has been shown that thioridazine used alone destroyed CSCs and induced autophagy [247], which was validated and confirmed recently in a dual therapy with temozolomide, using *i.e.* the bioinformatics and empirical analysis [243]. Mechanistically, such a process involved the increased activity of the AMPK signaling pathway, but also the enhanced Wnt pathway with the key protein – β-catenin [243].

3.2.3.2. Lung Cancer

In the studies on both cisplatin-sensitive and cisplatin-resistant lung cancer cell lines, thioridazine used alone was found to lead to programmed death of these cancer cells [240]. Intriguingly, a combination therapy with the use of thioridazine and cisplatin led also to a similar mechanism in ovarian cancer, resulting in a significant percentage of dead cells [240]. One of the reasons for the failure of lung cancer treatment is the presence of CSCs, a small sub-population of cancer cells associated with cancer progression, metastasis, resistance to the therapy applied, and tumor initiation [248, 249]; to eliminate CSCs, they should be either destroyed or differentiated [250]. Of note is that thioridazine increased the eradication of lung CSCs, both *in vitro* and *in vivo* [237]. The measurement of inhibition of CSCs activity was a decrease in expression of markers typical of this small sub-population of cancer cells, like Nanog, octamer-binding transcription factor 4 (Oct-4), and sex determining region Y-box (SOX) [237]. Thioridazine also improved the activity of some cytostatics (5-fluorouracil and cisplatin) used in an animal model [237].

Similar benefits regarding the effects of thioridazine on lung cancer have been observed by other authors [251]. Using the established stem-like lung cancer cells, thioridazine was identified to induce apoptosis of these cells *via* activation of caspases and through inhibition of the AKT-CDK2 signaling pathway [251]. The effects of thioridazine on lung CSCs were also studied on a mouse xenograft model; an inhibitory effect was found on both tumor initiation and its progression [251].

3.2.3.3. Ovarian Cancer

Although the standard surgical treatment combined with chemotherapy has been relatively successful, and more recently also with immunotherapy, ovarian cancer remains the most common cause of death among gynecological cancers [252]. This is the reason for the search for new strategies in the fight against this cancer. Interestingly, the positive effects of the use of thioridazine have been reported towards the established SKOV-3 ovarian cancer cell line [239]. Thioridazine reduced cell viability and induced apoptosis of these cancer cells by inhibiting the PI3K/AKT signaling pathway [239]. Furthermore, this agent reduced the activity of cyclin D1 and CDK4 by affecting the p16 and p21 proteins, resulting in cell cycle arrest at the G0/G1 phase [239]. The cytotoxic effect in SKOV-3 ovarian cancer cells was greater when cisplatin was combined with thioridazine [239].

This observation was similar to that made by other authors, suggesting the therapeutic potential of thioridazine in modulating chemoresistance. In a study on two established ovarian cancer cell lines, the combination of thioridazine and cisplatin led to the highest percentage of dead cells compared to thioridazine used alone [240]. The cell cycle also stopped at the G0/G1 phase, and the mechanism responsible for that was the activation of caspase 9 and Bax-2, as well as the reduction of expression of Bcl-2 [240]. The anticancer activity of thioridazine toward ovarian cancer was confirmed not only in the *in vitro* tests, but also in *in vivo* studies [236, 241]. The administration of thioridazine significantly inhibited (5-times) tumor growth and reduced its vascularization through the inhibition of the VEGFR2/PI3K/mTOR [241].

3.2.3.4. Other Types of Cancer

Among the other cancer cells that have been found to be efficiently targeted by thioridazine, cervical and endometrial ones should be mentioned as sensitive to the action of this psychiatric drug (15 μM), with similar patterns as those observed for cisplatin [238], besides colorectal [253] and gastric cancer cells [254]. In 2018, thioridazine was identified to inhibit self-renewal in some triple-negative breast cancer cells *via* DRD2-dependent STAT3 inhibition, with the IC_{50} values ranging from 2.3 μM to 6.1 μM, but induced independently G1 arrest of DRD2 [255]. Interestingly also, some reports observed the anticancer activity of thioridazine in combination with other agents. For example, thioridazine enhanced sensitivity to carboplatin in human head and neck cancer cells [256], tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in renal carcinoma cells [257], as well as the effects of medroxyprogesterone on the inhibition of proliferation and apoptotic promotion in endometrial cancer cells [258]. In addition, some other findings suggested that thioridazine combination therapy with loratadine might provide promising therapy for gastrointestinal cancer [259], while that with curcumin for head and neck squamous cell carcinoma [260]. Using another strategy, co-delivery of thioridazine and doxorubicin using polymeric micelles or nanoparticles could be effective for breast cancer treatment by targeting both cancer cells and CSCs [261, 262].

3.2.4. Trifluoperazine

Trifluoperazine (Fig. **1B**) is a long-established typical antipsychotic drug that has been used since the 1950s to treat schizophrenia, schizophrenia-like illnesses, but also non-psychotic anxiety (Table **1**) [263-265]. The administration of trifluoperazine may, however, result in movement disorders [266]. This drug has been extensively studied as a calmodulin and P-gp inhibitor [265]. As the regulation of both molecular targets plays a pivotal role in cellular proliferation, inflammation, neurodegeneration, and other pathological processes, including also cancer development, trifluoperazine has become the object of many studies in the direction of its anticancer activity (Table **1**) [265]. Indeed, according to a series of studies, trifluoperazine showed positive effects in treatment of various types of cancer; including breast cancer and glioblastoma (Table **1**), *via* induction of programmed cell death, reduction of migration and metastasis, inhibition of angiogenesis, CSCs suppression, as well as activation of the forkhead box O3 (FOXO3) transcription protein as the main events [267-272].

3.2.4.1. Breast Cancer

The key point for improving treatment outcomes for poorly promising triple-negative breast cancer variants is to inhibit metastases to various organs; about 50% of patients with this subtype of breast cancer have brain metastases [273]. The *in vitro* studies on three human triple-negative breast cancer cell lines showed that trifluoperazine possessed strong anticancer properties; it induced cell death by stopping the G0/G1 cell cycle [268]. Further, the *in vivo* studies in a mouse model showed similar trifluoperazine antitumor activity; intraperitoneal administration of this compound at various doses resulted in tumor reduction without apparent toxicity [268]. The main signaling pathway associated with this result was AKT-NF-κB [268]. The *in vivo* studies also suggested that trifluoperazine had the ability to significantly reduce the size of brain metastases by even more than 73% [268]. Of note is that the total survival time of trifluoperazine-treated mice was 22 days compared to 19 days in the control group, and this effect might be related to the ability of this antipsychotic to cross the blood-brain barrier [268].

The tests performed on triple-negative breast cancer cells also suggested that the use of different doses of trifluoperazine caused the inhibition of growth of these cancer cells, and led to their apoptosis [272]. The same human cancer cell lines were given to animals (nude mice), and the dose-dependent inhibition of tumor growth was also observed [272]. However, it has been found that the mechanism of the anticancer activity of trifluoperazine could be slightly different, and might be rather linked to the inhibition of the activity of AKT, which then promoted the nuclear localization of FOXO3 [272]. Recently, it has also been documented that trifluoperazine acted on stem-like cells of triple-negative breast cancer by inhibiting cell migration and cancer progression [269].

3.2.4.2. Glioblastoma

Interestingly, trifluoperazine has been reported to inhibit the development and invasion of glioma [267, 274]. Briefly, the beneficial effects of trifluoperazine were shown in both the *in vitro* and *in vivo* models [267]. In human glioblastoma cell line U87MG, trifluoperazine inhibited cell proliferation, motility and invasion [267]. On the other hand, the results of the *in vivo* experiments showed that the tumor volume decreased, and lung metastases were not found after trifluoperazine administration, compared to the control group [267]. Also, the dimensions of brain glioma implanted into the brain were reduced by even 75% [267].

Mechanistically, it has been proposed that the activity of this antipsychotic drug was strictly connected with its ability to bind to calmodulin [267]. Similar antiproliferative effects of the therapy with the use of trifluoperazine on glioblastoma cell lines have also been observed in another study; cell growth and proliferation were dose-dependent, and dopamine receptor signaling pathways were potential targets for pharmacological interventions [274].

With respect to very problematic invasion properties of glioblastoma, trifluoperazine was found to have beneficial effects against this characteristic feature of brain cancer [275]. Trifluoperazine activity in combination with irradiation was assessed *in vitro* and *in vivo* toward human glioblastoma cells; such dual therapy had an additive inhibitory effect on glioma cells, especially after intracranial implantation in mice [275]. It has been calculated that irradiation as an independent method extended animal survival (24.8 *vel* 29.7 days), while the addition of trifluoperazine affected the median survival (46.0 *vel* 29.7 days), and the authors believed that the positive effects of the use of trifluoperazine on sensitivity to radiation could be due to the disturbance of trifluoperazine-induced homologous recombination [275].

However, an ambiguous result of the trifluoperazine effects on glioma was presented in 2018. In both *in vitro* and *in vivo* studies, trifluoperazine administered at low concentrations (2-4 μM) was identified to cause rather increased cell proliferation and reduced apoptosis of cancer cells [276]. Therefore, the real therapeutic potential of this antipsychotic agent toward brain tumors needs to be developed, and requires confirmation in future studies.

3.2.4.3. Other Types of Cancer

The other types of cancer that might be destroyed after trifluoperazine administration include colorectal [277] and hepatocellular carcinoma [278]. From the mechanistic point of view, this psychiatric drug led to the down-regulation of the expression of CDK4, cyclin E1, antiapoptosis factor Bcl-2, proliferating cell nuclear antigen (PCNA), VEGF, up-regulation of the proapoptosis factor Bax, and increased nuclear localization of FOXO1 [277, 278], depending on the type of cancer studied.

Furthermore, using *in silico* drug screening by CMap that was followed by empirical validations, trifluoperazine was found to have a potential to be repurposed as an anti-CSCs agent that could overcome EGFR-tyrosine kinase inhibitor (TKI) as well as chemotherapy resistance in lung cancer [279]. The anti-lung cancer activity of trifluoperazine was also confirmed by other teams [280], and further, as this compound might be capable of inhibiting one or more elements of the DNA double-strand break (DSB) repair machinery, thereby it could increase the cytotoxicity of bleomycin in non-small cell lung cancer [281].

Anyway, taking into account the sensitizing effects of trifluoperazine, it might potentiate cisplatin cytotoxicity in human ovarian carcinoma cell lines [282], while trifluoperazine combined with ketoconazole or doxorubicin could be effective toward murine T-cell lymphomas or might induce the selection of tumor cells with the MDR phenotype, respectively [283, 284]. On the other hand, epirubicin plus trifluoperaxine dual therapy did not show an improvement in response and survival rate when compared to the results with other treatment schedules without anti-MDR agents [285].

4. CHALLENGES AND LIMITATIONS ASSOCIATED WITH REPURPOSING OF PSYCHIATRIC AGENTS

As highlighted above, antidepressants and antipsychotics have the potential to be repurposed in oncology. They might be used in the preventive treatment and/or to support cancer care, as they are the elements of a series of ongoing or completed clinical trials (Table **2**). Moreover, some reports have suggested that selected psychiatric drugs could directly inhibit the growth of cancer cells (Table **1**), and finally lead to their death *via* apoptosis or autophagy. However, challenges and limitations still exist in the possible repurposing of these drugs in oncology, such as their potential carcinogenicity, controversial clinical studies and poor tolerance, all of which have to be carefully considered prior to their further clinical trials as well as applications.

Firstly, with respect to the preventive role of psychiatric drugs, the findings on the positive effects of these drugs on cancer risk found in the clinical studies seem to be slightly controversial. On one hand, some of the studies showed that the use of psychiatric drugs was linked with a reduced risk of various cancers, including hepatocellular carcinoma and ovarian cancer [112, 286], but on the other hand, other data indicated a completely different trend. For example, the use of antipsychotics was suggested to cause higher breast cancer and acute myeloid leukemia (AML) incidence compared to patients with schizophrenia or other psychiatric disorders that did not receive these agents [287-291]. Thus, it is extremely difficult to draw une-

Table 2. The ongoing and completed clinical trials in cancer patients with the use of selected antidepressant and antipsychotic agents (ClinicalTrials.gov; on-line access April 15th, 2020).

Compound	Title of clinical trial	Study description	Status	Results	ClinicalTrials.gov identifier
Citalopram	Pilot study to evaluate individualized choice of antidepressants in patients with cancer	Testing the hypothesis that mirtazapine and citalopram are effective treatment for MDD in cancer patients	Completed	N/P[a)]	NCT01725048
	Tamoxifen in women with breast cancer and in women at high-risk of breast cancer who are receiving venlafaxine, citalopram, escitalopram, gabapentin, or sertraline	Studying levels of tamoxifen in the blood of women with breast cancer and in women at high risk of breast cancer who are receiving tamoxifen together with SSRIs and SNRIs	Active, not recruiting	N/P[a)]	NCT00667121
Fluoxetine	Combination chemotherapy plus fluoxetine in treating patients with advanced or recurrent non-small cell lung cancer	Testing the efficacy of fluoxetine to improve patient's quality of life during chemotherapy	Completed	N/P[a)]	NCT00005850
Sertraline	A proof-of-concept clinical trial assessing the safety of the coordinated undermining of survival paths by 9 repurposed drugs combined with metronomic temozolomide (CUSP9v3 treatment protocol) for recurrent glioblastoma	Assessing the safety of the coordinated undermining of survival paths by 9 repurposed drugs combined with metronomic temozolomide for recurrent glioblastoma	Active, not recruiting	N/P[a)]	NCT02770378
	Sertraline and cytosine arabinoside in adults with relapsed and refractory AML	Determining the feasibility, safety, and toxicity of administering sertraline in combination with timed-sequential cytosine arabinoside in adults with relapsed and refractory AML	Recruiting	N/P[a)]	NCT02891278
Chlorpromazine	Haloperidol with or without chlorpromazine in treating delirium in patients with advanced, metastatic, or recurrent cancer	Studying how haloperidol with or without chlorpromazine works in treating delirium (loss of contact with reality) in patients with cancer that has spread to other parts of the body or has come back, as both agents may control the symptoms of delirium in patients with cancer	Active, not recruiting	N/P[a)]	NCT03021486
	Repurposing chlorpromazine in the treatment of glioblastoma (RACTAC)	Evaluation of the addition of chlorpromazine to the first-line therapeutic protocol, *i.e.* maximal well-tolerated surgical resection followed by radiotherapy	Recruiting	N/P[a)]	NCT04224441

(Table 2) contd….

Compound	Title of clinical trial	Study description	Status	Results	ClinicalTrials.gov identifier
		plus concomitant and adjuvant chemotherapy with temozolomide, in newly diagnosed glioblastoma multiforme patients			
Thioridazine	Safety study of thioridazine in combination with cytarabine to treat relapsed or refractory acute myeloid leukemia (THORIDAL)	Investigation of the safety of using thioridazine in addition to cytarabine in elderly patients with relapsed or refractory AML	Completed	Methodology: 13 patients, 55 years and older with AML; thioridazine (TDZ) given orally at 3 doses (25, 50, or 100 mg) every 6 h for 21 days; cytarabine administered on days 6 to 10. Results: 11 patients completed a 5-day lead-in with TDZ; 8 patients demonstrated a 19% to 55% reduction in blast levels, whereas 3 patients displayed progressive disease; side effects included QTc interval prolongation in 1 patient and neurological events in 2 patients at 25 and 100 mg TDZ, respectively [307]	NCT02096289

[a)]N/P – no results posted

quivocal conclusions from this type of research, as the results obtained may depend on many factors and variables, including the number, condition and lifestyle (smoking, diet, comorbidities, *etc*.) of individuals included in the tests or the type and dosage of psychiatric therapeutics used. Furthermore, it should be emphasized that retrospective analysis, such as meta-analysis and trial sequential analysis, would not be used to prove that agent X causes effect Y [1]. Of course, the connections might and should be reported, as the prospective data are needed to show causation, but even then, the readers have to be aware of inherent biases [1].

Secondly, it is extremely important for cancer patients to choose a psychiatric drug that will work selectively to reduce the possible increase in adverse side effects and the decrease in the efficiency of other chemotherapeutics used [292], as such individuals could be more vulnerable to any negative drug-drug interactions with respect to their physical fragilities, such as young/advanced age, loss of weight, poor nutrition, and other medical conditions, but also to iatrogenic disorders, possible enzyme deficit as well as multimedication [293].

Antidepressants may interact with anticancer drugs *via* pharmacokinetic/pharmacodynamic mechanisms that are independent of the pharmacologic properties responsible for their therapeutic efficacy [294]. In this context, the antidepressants that inhibit strongly the CYP2D6 enzymes seem to be particularly inadvisable, as they may increase the risk of cancer recurrence, adversely affecting well-being as well as overall survival; strong inhibitors of CYP2D6 should be thus avoided in patients treated for example with tamoxifen (Fig. **2A**), especially those with poor metabolizer phenotype of CYP2D6 [24, 94]. Indeed, some studies suggested that the use of paroxetine (Fig. **1B**) identified as a strong CYP2D6 inhibitor during tamoxifen treatment could be linked with an increased risk of death from breast cancer [295].

The consequence of survival of cancer patients is still controversial; although some reports indicated a higher risk of recurrence of breast cancer in patients who receive tamoxifen as well as CYP2D6-inhibiting drugs [295-297], more recent data had not confirmed these effects [298, 299]. It should also be stressed here that the CYP2D6 enzyme is known to be actively involved in metabolizing a series of psychiatric drugs, such as thioridazine [234]. Thus, standard doses of some antidepressants and antipsychotics could lead to higher drug levels in the plasma, and increase the risk of cardiac arrhythmias in patients with low CYP2D6 activity (~7% of the population) [234].

On the other hand, analgesic drugs, like codeine, fentanyl, hydrocodone, oxycodone and tramadol, and antiemetics of 5-HT_3 receptor antagonists are usually used in cancer patients as palliative treatment [94], but such agents can interact with serotonergic antidepressants as well, and thus increase the risk of serotonin syndrome [24]. For example, as tramadol is metabolized by CYP2D6 isoenzyme to its active metabolite – *O*-desmethyltramadol (Fig. **2B**), the simultaneous use of this drug in combination with an unsuitable antidepressant can lead to the abolition of the analgesic effect of tramadol [300].

Thirdly, both psychiatric and anticancer drugs have, in general, a very narrow therapeutic window, and therefore even subtle variations in their plasmic concentrations might result in subtherapeutic or even toxic effects [301]. For this reason, not only the observed therapeutic effect, but also the concentration of the psychiatric drug used to induce such an effect is important, and should be carefully analyzed. For instance, paroxetine (Fig. **1B**) at the concentration of 10 μM and 30 μM was found to induce cell death of two breast cancer cell lines (MCF-7 and MDA-MB-231) [164], but these concentrations seemed to be higher than that of therapeutic concentration of paroxetine, and thus they would not be expected to induce significant cell death *in vivo*. As indicated for patients with MDD, the therapeutic reference range for plasma concentrations of paroxetine is 20-60 ng mL^{-1} when 10–40 mg per day of paroxetine for 6 weeks was administered as a single daily dose; such a dose could be however slightly increased in some patients not responding to the therapy applied [302]. Of course, it is not possible to simply translate the results of *in vitro* tests into what will be observed in *in vivo* experiments, just as it is impossible to translate the pharmacological effects observed in mice or rats to those in humans. Nevertheless, as the psychiatric drugs can be used in the appropriate doses over a long period of time to obtain their effectiveness, such long-term exposure using a low dose of an antidepressant or antipsychotic agent might induce expected death of cancer cells *in vivo*.

Finally, the use of psychiatric drugs might be connected with a risk of hepatotoxicity to varying degrees [303], depending on the agent used. For example, imipramine and iproniazid (Fig. **1B**) were reported frequently to induce liver injury, while citalopram and paroxetine (Fig. **1B**) were linked with a lower risk of hepatotoxicity [303]. Simultaneously, drug-induced liver injury is one of the most common reasons to terminate the development of new drug candidates and/or remove them from the market after approval [304]. Moreover, long-term administration of antidepressants and antipsychotic agents might result in a series of side effects; for example, patients treated with first-generation antipsychotics are more likely to experience EPSs, while the main problems connected with the use of second-generation antipsychotic agents are weight gain and metabolic disorders [305, 306]. Other possible side effects include cardiac arrhythmia, postural hypotension, prolactin increase, QTc prolongation (the time taken for the heart ventricles to depolarize and repolarize), sedation, and sexual dysfunction [306]. Therefore, all aspects discussed above should be carefully considered, and further research would be required to balance the ratio between benefits and risks of additional clinical complications.

CONCLUSION

The long history of clinical use of both antidepressant and antipsychotic drugs, the existing clinical results, toxicology profiles, and reasonable prices make this large group of therapeutics very promising candidates for repurposing in oncology. It has been reported that selected psychiatric drugs may arrest the proliferation of cancer cells, and induce their apoptosis or autophagy through various mechanisms of action, both *in vitro* and *in vivo*. Taking into account their good bioavailability in the brain, particularly interesting seems to be the potent efficiency of psychiatric drugs toward glioblastoma multiforme as well as other brain tumors. Nevertheless, as the anticancer therapies unfortunately lack alternative strategies to overcome the problem of chemoresistance, the potential of antipsychotics to sensitize various cancer cells to the action of cytostatics is also of great value. Importantly, antidepressants and antipsychotic drugs are currently under evaluation in a series of clinical trials to evaluate their positive effects in supportive care of cancer patients.

Table 3. Summary of the anticancer activity of psychiatric drugs reviewed in this article.

Primary site	Cancer type	Antidepressant agents				Antipsychotic agents			
		Citalopram	Fluoxetine	Paroxetine	Sertraline	Chlorpromazine	Pimozide	Thioridazine	Trifluoperazine
Bone	Osteosarcoma			+			+		
Brain and nervous system	Glioblastoma						+	+	+
	Glioma		+	+	+	+			
	Neuroblastoma	+	+	+					
Chest and respiratory system	Breast cancer		+	+	+	+	+	+	+
	Lung cancer		+		+			+	+
Digestive system	Colon cancer	+	+	+	+				
	Colorectal carcinoma	+	+	+		+		+	+
	Gastric cancer							+	
	Hepatocellular carcinoma	+	+		+		+		+
Female reproductive system	Cervical cancer		+			+		+	
	Endometrial cancer							+	
	Ovarian cancer		+					+	
Head and neck	Oral cancer			+	+				
Hematopoietic system	Acute myeloid leukemia	+							
	Burkitt lymphoma		+						
Skin	Melanoma				+				
Other	Prostate cancer		+	+	+		+		
	Soft tissue sarcoma		+						

Besides the original medical indication of psychiatric drugs to treat depression, schizophrenia as well as other depressive disorders, and their potent cytotoxicity towards cancer cells, some of these compounds have provided additional benefits for cancer chemotherapy, including the possible preventive role in cancer development and therapeutic effects against chemotherapy-related adverse side effects.

Although several authors have reported the great potential of antidepressants and antipsychotic agents to be repurposed in oncology, a list of challenges and limitations still exist, and there is a need to consider all

of them prior to their further clinical application in cancer treatment. It includes possible carcinogenetic properties and negative drug-drug interactions, narrow therapeutic windows and a wide range of adverse effects if used for a long time.

Nevertheless, there are actually no completely safe drugs available for the therapy of cancer, and the commonly used cytostatic drugs that have promising effects on various types of cancer might exhibit lethal side effects as well. In this context, antipsychotics could be relatively safe and effective agents for severe depression in cancer patients. A series of recent studies have revealed significant anticancer activity of these compounds against various types of cancer cells (Table **3**), used alone or in combination with well-known anticancer drugs. These data clearly indicate that both antidepressants and antipsychotic drugs might be potentially new anticancer chemotherapeutics rather than only the treatment options for cancer patients with depression or schizophrenia, and the proper use of these drugs could be helpful for the effective treatment of cancer regardless of mental disorders.

Of course, more advanced studies are extremely needed to confirm such observations, as well as to find the best structures from a broad library of antipsychotic drugs to be used exclusively in anticancer therapy. Moreover, although the repurposing strategy seems to be an extremely attractive source of new alternatives in cancer treatment, selected psychiatric drugs that have the potential to be repurposed in oncology should be rather used as elements of adjunct modes of treatment, and combined with well-established anticancer therapeutic modalities, but probably not in the form of monotherapy. On the other hand, because antidepressants and antipsychotic drugs misuse can lead to severe intoxication and even death, the experimental studies, both *in vitro* and *in vivo*, need to be performed to help establish the actual field of potential reproducibility, prior to the further examinations of these agents in clinical trials. Anyway, we suppose that through chemosensitization and direct effects of antipsychotics against cancer cells, these compounds could be successfully repurposed in oncological indications in the near future.

LIST OF ABBREVIATIONS

5-HTs	=	5-Hydroxytryptamine receptors
$\Delta\Psi_m$	=	Mitochondrial membrane potential
ADMET	=	Absorption, distribution, metabolism, elimination and toxicity
AML	=	Acute myeloid leukemia
AMPK	=	AMP-activated protein kinase
CcO	=	Cytochrome c oxidase
CDK2	=	Cyclin-dependent kinase 2
CDK4	=	Cyclin-dependent kinase 4
CDKs	=	Cyclin-dependent kinases
CKIs	=	Cyclin-dependent kinase inhibitors
CMap	=	Connectivity Map
CNS	=	Central nervous system
COVID-19	=	Coronavirus disease 2019
CSCs	=	Cancer stem cells
CYP	=	Cytochrome P450
DRD2	=	Dopamine receptor D2
DSB	=	Double-strand break
EAT	=	Ehrilch ascites tumor
EGFR	=	Epidermal growth factor receptor
EpCAM	=	Epithelial cell adhesion molecule
EPSs	=	Extra-pyramidal symptoms
ER	=	Endoplasmic reticulum
ERK	=	Extracellular signal-related kinases
FAK	=	Focal adhesion kinase
FDA	=	Food and Drug Administration
FOXO3	=	Forkhead box O3
HIF-1α	=	Hypoxia-inducible factor 1α
ID1	=	Inhibitor of DNA binding 1
JNK	=	c-Jun *N*-terminal kinase
MAOIs	=	Monoamine oxidase inhibitors
MAPK	=	Mitogen-activated protein kinase
MDD	=	Major depressive disorder
MDR	=	Multi-drug resistance
MMP	=	Matrix metalloproteinase
MRSA	=	Methicillin-resistant *Staphylococcus aureus*
MSSA	=	Methicillin-sensitive *Staphylococcus aureus*
mTOR	=	Mechanistic target of rapamycin
NF-κB	=	Nuclear factor κ-light-chain-enhancer of activated B

Oct-4	=	Octamer-binding transcription factor 4
P-gp	=	P-glycoproteins
PARP1	=	Poly-ADP-ribose polymerase 1
PCNA	=	Proliferating cell nuclear antigen
PI3K	=	Phosphatidylinositol 3-kinase
PMDDs	=	Premenstrual dysphoric disorders
PS	=	Phosphatidylserine
Ran	=	Ras-related nuclear
ROS	=	Reactive oxygen species
SERM	=	Selective estrogen receptor modulators
SIRT1	=	Sirtuin 1
SNRIs	=	Serotonin-norepinephrine reuptake inhibitors
SOD	=	Superoxide dismutase
SOX	=	Sex determining region Y-box
SSRIs	=	Selective serotonin reuptake inhibitors
STAT3	=	Signal transducers and activators of transcription 3
TCAs	=	Tricyclic antidepressants
TKI	=	Tyrosine kinase inhibitor
TNF	=	Tumor necrosis factor
TRAIL	=	Tumor necrosis factor-related apoptosis-inducing ligand
USP1	=	Ubiquitin specific peptidase 1
VEGF	=	Vascular endothelial growth factor
VEGFR2	=	VEGF receptor 2
VRE	=	Vancomycin-resistant enterococci

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

M.A. wishes to acknowledge the Polish Science Center (NCN) and the Polish National Agency for Academic Exchange (NAWA) for the scholarships under the UWERTURA (2019/32/U/ST4/00092) and the BEKKER program (PPN/BEK/2019/1/00034), respectively, and the Polish Ministry of Science and Higher Education (MNiSW) for the scholarship for outstanding young scientists in the years 2020−2023 (STYP/15/1665/E-336/2020).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors like to thank the Polish Science Center (NCN), the Polish National Agency for Academic Exchange (NAWA) and the Polish Ministry of Science and Higher Education for their support and scholarships.

REFERENCES

[1] Antoszczak, M.; Markowska, A.; Markowska, J.; Huczyński, A. Old wine in new bottles: Drug repurposing in oncology. *Eur. J. Pharmacol.,* **2020**, *866*172784 http://dx.doi.org/10.1016/j.ejphar.2019.172784 PMID: 31730760

[2] Prasad, V.; Mailankody, S. Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern. Med.,* **2017**, *177*(11), 1569-1575. http://dx.doi.org/10.1001/jamainternmed.2017.3601 PMID: 28892524

[3] Abdelaleem, M.; Ezzat, H.; Osama, M.; Megahed, A.; Alaa, W.; Gaber, A.; Shafei, A.; Refaat, A. Prospects for repurposing CNS drugs for cancer treatment. *Oncol. Rev.,* **2019**, *13*(1), 411. http://dx.doi.org/10.4081/oncol.2019.411 PMID: 31044029

[4] Niraula, S.; Seruga, B.; Ocana, A.; Shao, T.; Goldstein, R.; Tannock, I.F.; Amir, E. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. *J. Clin. Oncol.,* **2012**, *30*(24), 3012-3019. http://dx.doi.org/10.1200/JCO.2011.40.3824 PMID: 22802313

[5] Huang, J.; Zhao, D.; Liu, Z.; Liu, F. Repurposing psychiatric drugs as anti-cancer agents. *Cancer Lett.,* **2018**, *419*, 257-265. http://dx.doi.org/10.1016/j.canlet.2018.01.058 PMID: 29414306

[6] Mullard, A. 2015 FDA drug approvals. *Nat. Rev. Drug Discov.,* **2016**, *15*(2), 73-76. http://dx.doi.org/10.1038/nrd.2016.15 PMID: 26837582

[7] Jiang, X.; Lu, W.; Shen, X.; Wang, Q.; Lv, J.; Liu, M.; Cheng, F.; Zhao, Z.; Pang, X. Repurposing sertraline sensitizes non-small cell lung cancer cells to erlotinib by inducing autophagy. *JCI Insight,* **2018**, *3*(11)e98921 http://dx.doi.org/10.1172/jci.insight.98921 PMID: 29875309

[8] Ashburn, T.T.; Thor, K.B. Drug repositioning: identifying and developing new uses for existing drugs. *Nat. Rev. Drug Discov.,* **2004**, *3*(8), 673-683. http://dx.doi.org/10.1038/nrd1468 PMID: 15286734

[9] Chong, C.R.; Sullivan, D.J., Jr New uses for old drugs. *Nature,* **2007**, *448*(7154), 645-646. http://dx.doi.org/10.1038/448645a PMID: 17687303

[10] Dudley, J.T.; Sirota, M.; Shenoy, M.; Pai, R.K.; Roedder, S.; Chiang, A.P.; Morgan, A.A.; Sarwal, M.M.; Pasricha, P.J.; Butte, A.J. Computational repositioning of the anticonvul-

sant topiramate for inflammatory bowel disease. *Sci. Transl. Med.,* **2011**, *3*(96)96ra76 http://dx.doi.org/10.1126/scitranslmed.3002648 PMID: 21849664

[11] Langedijk, J.; Mantel-Teeuwisse, A.K.; Slijkerman, D.S.; Schutjens, M.H. Drug repositioning and repurposing: terminology and definitions in literature. *Drug Discov. Today,* **2015**, *20*(8), 1027-1034. http://dx.doi.org/10.1016/j.drudis.2015.05.001 PMID: 25975957

[12] Padhy, B.M.; Gupta, Y.K. Drug repositioning: re-investigating existing drugs for new therapeutic indications. *J. Postgrad. Med.,* **2011**, *57*(2), 153-160. http://dx.doi.org/10.4103/0022-3859.81870 PMID: 21654146

[13] Sleigh, S.H.; Barton, C.L. Repurposing strategies for therapeutics. *Pharmaceut. Med.,* **2010**, *24*, 151-159. http://dx.doi.org/10.1007/BF03256811

[14] Singh, N.; Halliday, A.C.; Thomas, J.M.; Kuznetsova, O.V.; Baldwin, R.; Woon, E.C.Y.; Aley, P.K.; Antoniadou, I.; Sharp, T.; Vasudevan, S.R.; Churchill, G.C. A safe lithium mimetic for bipolar disorder. *Nat. Commun.,* **2013**, *4*, 1332. http://dx.doi.org/10.1038/ncomms2320 PMID: 23299882

[15] Li, Y.Y.; Jones, S.J. Drug repositioning for personalized medicine. *Genome Med.,* **2012**, *4*(3), 27. http://dx.doi.org/10.1186/gm326 PMID: 22494857

[16] Hernandez, J.J.; Pryszlak, M.; Smith, L.; Yanchus, C.; Kurji, N.; Shahani, V.M.; Molinski, S.V. Giving drugs a second chance: Overcoming regulatory and financial hurdles in repurposing approved drugs as cancer therapeutics. *Front. Oncol.,* **2017**, *7*, 273. http://dx.doi.org/10.3389/fonc.2017.00273 PMID: 29184849

[17] Issa, N.T.; Kruger, J.; Byers, S.W.; Dakshanamurthy, S. Drug repurposing a reality: from computers to the clinic. *Expert Rev. Clin. Pharmacol.,* **2013**, *6*(2), 95-97. http://dx.doi.org/10.1586/ecp.12.79 PMID: 23473587

[18] Franks, M.E.; Macpherson, G.R.; Figg, W.D. Thalidomide. *Lancet,* **2004**, *363*(9423), 1802-1811. http://dx.doi.org/10.1016/S0140-6736(04)16308-3 PMID: 15172781

[19] Kasznicki, J.; Sliwinska, A.; Drzewoski, J. Metformin in cancer prevention and therapy. *Ann. Transl. Med.,* **2014**, *2*(6), 57. PMID: 25333032

[20] Colson, P.; Rolain, J.M.; Lagier, J.C.; Brouqui, P.; Raoult, D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int. J. Antimicrob. Agents,* **2020**, *55*(4)105932 http://dx.doi.org/10.1016/j.ijantimicag.2020.105932 PMID: 32145363

[21] Touret, F.; de Lamballerie, X. Of chloroquine and COVID-19. *Antiviral Res.,* **2020**, *177*104762 http://dx.doi.org/10.1016/j.antiviral.2020.104762 PMID: 32147496

[22] Gao, J.; Tian, Z.; Yang, X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci. Trends,* **2020**, *14*(1), 72-73. http://dx.doi.org/10.5582/bst.2020.01047 PMID: 32074550

[23] Caly, L.; Druce, J.D.; Catton, M.G.; Jans, D.A.; Wagstaff, K.M. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. *Antiviral Res.,* **2020**, *178*104787 http://dx.doi.org/10.1016/j.antiviral.2020.104787 PMID: 32251768

[24] Grassi, L.; Nanni, M.G.; Rodin, G.; Li, M.; Caruso, R. The use of antidepressants in oncology: a review and practical tips for oncologists. *Ann. Oncol.,* **2018**, *29*(1), 101-111. http://dx.doi.org/10.1093/annonc/mdx526 PMID: 29272358

[25] Rodin, G.; Katz, M.; Lloyd, N.; Green, E.; Mackay, J.A.; Wong, R.K.S. Treatment of depression in cancer patients. *Curr. Oncol.,* **2007**, *14*(5), 180-188. http://dx.doi.org/10.3747/co.2007.146 PMID: 17938701

[26] Grassi, L.; Nanni, M.G.; Uchitomi, Y.; Riba, M. Pharmacotherapy of depression in people with cancer.*Depression and Cancer*; Kissane, D.; Maj, M.; Sartorius, N., Eds.; Wiley: London, **2011**, pp. 151-175.

[27] Li, M.; Fitzgerald, P.; Rodin, G. Evidence-based treatment of depression in patients with cancer. *J. Clin. Oncol.,* **2012**, *30*(11), 1187-1196. http://dx.doi.org/10.1200/JCO.2011.39.7372 PMID: 22412144

[28] Pottegård, A.; García Rodríguez, L.A.; Rasmussen, L.; Damkier, P.; Friis, S.; Gaist, D. Use of tricyclic antidepressants and risk of glioma: a nationwide case-control study. *Br. J. Cancer,* **2016**, *114*(11), 1265-1268. http://dx.doi.org/10.1038/bjc.2016.109 PMID: 27115466

[29] Lee, W.Y.; Lee, W.T.; Cheng, C.H.; Chen, K.C.; Chou, C.M.; Chung, C.H.; Sun, M.S.; Cheng, H.W.; Ho, M.N.; Lin, C.W. Repositioning antipsychotic chlorpromazine for treating colorectal cancer by inhibiting sirtuin 1. *Oncotarget,* **2015**, *6*(29), 27580-27595. http://dx.doi.org/10.18632/oncotarget.4768 PMID: 26363315

[30] Jahchan, N.S.; Dudley, J.T.; Mazur, P.K.; Flores, N.; Yang, D.; Palmerton, A.; Zmoos, A.F.; Vaka, D.; Tran, K.Q.; Zhou, M.; Krasinska, K.; Riess, J.W.; Neal, J.W.; Khatri, P.; Park, K.S.; Butte, A.J.; Sage, J. A drug repositioning approach identifies tricyclic antidepressants as inhibitors of small cell lung cancer and other neuroendocrine tumors. *Cancer Discov.,* **2013**, *3*(12), 1364-1377. http://dx.doi.org/10.1158/2159-8290.CD-13-0183 PMID: 24078773

[31] Pereira, V.S.; Hiroaki-Sato, V.A. A brief history of antidepressant drug development: from tricyclics to beyond ketamine. *Acta Neuropsychiatr.,* **2018**, *30*(6), 307-322. http://dx.doi.org/10.1017/neu.2017.39 PMID: 29388517

[32] López-Muñoz, F.; Alamo, C. Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. *Curr. Pharm. Des.,* **2009**, *15*(14), 1563-1586. http://dx.doi.org/10.2174/138161209788168001 PMID: 19442174

[33] Hillhouse, T.M.; Porter, J.H. A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp. Clin. Psychopharmacol.,* **2015**, *23*(1), 1-21. http://dx.doi.org/10.1037/a0038550 PMID: 25643025

[34] López-Muñoz, F.; Alamo, C.; Juckel, G.; Assion, H.J. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part I: monoamine oxidase inhibitors. *J. Clin. Psychopharmacol.,* **2007**, *27*(6), 555-559. http://dx.doi.org/10.1097/jcp.0b013e3181bb617 PMID: 18004120

[35] Pletscher, A. The discovery of antidepressants: a winding path. *Experientia,* **1991**, *47*(1), 4-8. http://dx.doi.org/10.1007/BF02041242 PMID: 1999242

[36] Domino, E.F. History of modern psychopharmacology: a personal view with an emphasis on antidepressants. *Psychosom. Med.,* **1999**, *61*(5), 591-598.

http://dx.doi.org/10.1097/00006842-199909000-00002 PMID: 10511010

[37] Fangmann, P.; Assion, H.J.; Juckel, G.; González, C.A.; López-Muñoz, F. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part II: tricyclics and tetracyclics. *J. Clin. Psychopharmacol.,* **2008**, *28*(1), 1-4. http://dx.doi.org/10.1097/jcp.0b013e3181627b60 PMID: 18204333

[38] Abbing-Karahagopian, V.; Huerta, C.; Souverein, P.C.; de Abajo, F.; Leufkens, H.G.; Slattery, J.; Alvarez, Y.; Miret, M.; Gil, M.; Oliva, B.; Hesse, U.; Requena, G.; de Vries, F.; Rottenkolber, M.; Schmiedl, S.; Reynolds, R.; Schlienger, R.G.; de Groot, M.C.; Klungel, O.H.; van Staa, T.P.; van Dijk, L.; Egberts, A.C.; Gardarsdottir, H.; De Bruin, M.L. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. *Eur. J. Clin. Pharmacol.,* **2014**, *70*(7), 849-857. http://dx.doi.org/10.1007/s00228-014-1676-z PMID: 24793010

[39] Shaw, D.M.; Camps, F.E.; Eccleston, E.G. 5-Hydroxytryptamine in the hind-brain of depressive suicides. *Br. J. Psychiatry,* **1967**, *113*(505), 1407-1411. http://dx.doi.org/10.1192/bjp.113.505.1407 PMID: 6078496

[40] Cowen, P.J.; Browning, M. What has serotonin to do with depression? *World Psychiatry,* **2015**, *14*(2), 158-160. http://dx.doi.org/10.1002/wps.20229 PMID: 26043325

[41] Blier, P.; El Mansari, M. Serotonin and beyond: therapeutics for major depression. *Philos. Trans. R. Soc. Lond. B Biol. Sci.,* **2013**, *368*(1615)20120536 http://dx.doi.org/10.1098/rstb.2012.0536 PMID: 23440470

[42] Wong, D.T.; Bymaster, F.P.; Engleman, E.A. Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication. *Life Sci.,* **1995**, *57*(5), 411-441. http://dx.doi.org/10.1016/0024-3205(95)00209-O PMID: 7623609

[43] Wong, D.T.; Perry, K.W.; Bymaster, F.P. Case history: the discovery of fluoxetine hydrochloride (Prozac). *Nat. Rev. Drug Discov.,* **2005**, *4*(9), 764-774. http://dx.doi.org/10.1038/nrd1821 PMID: 16121130

[44] Millan, M.J. Multi-target strategies for the improved treatment of depressive states: Conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol. Ther.,* **2006**, *110*(2), 135-370. http://dx.doi.org/10.1016/j.pharmthera.2005.11.006 PMID: 16522330

[45] Ban, T.A. Pharmacotherapy of depression: a historical analysis. *J. Neural Transm. (Vienna),* **2001**, *108*(6), 707-716. http://dx.doi.org/10.1007/s007020170047 PMID: 11478422

[46] Fava, M.; Rush, A.J.; Thase, M.E.; Clayton, A.; Stahl, S.M.; Pradko, J.F.; Johnston, J.A. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim. Care Companion J. Clin. Psychiatry,* **2005**, *7*(3), 106-113. http://dx.doi.org/10.4088/PCC.v07n0305 PMID: 16027765

[47] Stahl, S.M.; Pradko, J.F.; Haight, B.R.; Modell, J.G.; Rockett, C.B.; Learned-Coughlin, S. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim. Care Companion J. Clin. Psychiatry,* **2004**, *6*(4), 159-166. http://dx.doi.org/10.4088/PCC.v06n0403 PMID: 15361919

[48] Papakostas, G.I. Serotonin norepinephrine reuptake inhibitors: Spectrum of efficacy in major depressive disorder. *Prim. Psychiatry,* **2009**, *16*, 16-24.

[49] Gibb, A.; Deeks, E.D. Vortioxetine: first global approval. *Drugs,* **2014**, *74*(1), 135-145. http://dx.doi.org/10.1007/s40265-013-0161-9 PMID: 24311349

[50] Hashimoto, K. Rapid-acting antidepressant ketamine, its metabolites and other candidates: A historical overview and future perspective. *Psychiatry Clin. Neurosci.,* **2019**, *73*(10), 613-627. http://dx.doi.org/10.1111/pcn.12902 PMID: 31215725

[51] U.S. Food & Drug Administration. *FDA Newsroom – Press Announcements.,* https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified2020 [(Access ed March 24, 2020).];

[52] Shen, W.W. A history of antipsychotic drug development. *Compr. Psychiatry,* **1999**, *40*(6), 407-414. http://dx.doi.org/10.1016/S0010-440X(99)90082-2 PMID: 10579370

[53] Reinhardt, C.; Travis, A.S. *Heinrich Caro and the creation of modern chemical industry,* 1st ed; Springer: Netherlands, **2000**. http://dx.doi.org/10.1007/978-94-015-9353-3

[54] Müller, O.; Lu, G.; Jahn, A.; Mockenhaupt, F.P. How worthwhile is methylene blue as a treatment of malaria? *Expert Rev. Anti Infect. Ther.,* **2019**, *17*(7), 471-473. http://dx.doi.org/10.1080/14787210.2019.1634545 PMID: 31237457

[55] Okafor, C.O. The chemistry and applications of angular phenothiazine derivatives. *Dyes Pigments,* **1986**, *7*, 249-287. http://dx.doi.org/10.1016/0143-7208(86)85013-6

[56] Zirkle, C.L. The role of serendipity in drug discovery. In: *Dialogues Clin Neurosci*; , **1973**; 8, pp. 335-344.

[57] Gilman, H.; van Ess, P.R.; Shirley, D.A. The metalation of 10-phenylphenothiazine and of 10-ethylphenothiazine. *J. Am. Chem. Soc.,* **1944**, *66*, 1214-1216. http://dx.doi.org/10.1021/ja01235a042

[58] Ban, T.A. The role of serendipity in drug discovery. *Dialogues Clin. Neurosci.,* **2006**, *8*(3), 335-344. PMID: 17117615

[59] Pichot, P. The discovery of chlorpomazine and the place of psychopharmacology in the history of psychiatry.*The Psychopharmacologists*; Healy, D., Ed.; Chapman & Hall: New York, NY, **1996**, pp. 1-27.

[60] Ban, T.A. Fifty years chlorpromazine: a historical perspective. *Neuropsychiatr. Dis. Treat.,* **2007**, *3*(4), 495-500. PMID: 19300578

[61] Pöldinger, W.; Wider, F. *Index psychopharmacorum*; Huber: Canada, **1990**.

[62] Irtelli, F. *Psychosis*; Biopsychosocial and Relational Perspectives. IntechOpen, **2018**.

[63] Abou-Setta, A.M.; Mousavi, S.S.; Spooner, C.; Schouten, J.R.; Pasichnyk, D.; Armijo-Olivo, S.; Beaith, A.; Seida, J.C.; Dursun, S.; Newton, A.S.; Hartling, L. First-generation versus second-generation antipsychotics in adults: Comparative effectiveness. *Rockville (MD): Agency for Healthcare Research and Quality (US); Comparative Effectiveness Reviews, No. 63,* https://www.ncbi.nlm.nih.gov/books/NBK107254/2020 [(Access ed March 27, 2020).];

[64] Colvin, C.L.; Tankanow, R.M. Pimozide: use in Tourette's syndrome. *Drug Intell. Clin. Pharm.,* **1985**, *19*(6), 421-424. http://dx.doi.org/10.1177/106002808501900602 PMID: 3891283

[65] Carpenter, W.T., Jr; Davis, J.M. Another view of the history of antipsychotic drug discovery and development. *Mol. Psychiatry,* **2012**, *17*(12), 1168-1173. http://dx.doi.org/10.1038/mp.2012.121 PMID: 22889923

[66] Steck, H. Le syndrome extrapyramidal et diencephalique au Largactil et au Serpasil. *Ann. Med. Psychol. (Paris),* **1954**, *112*, 737-743. PMID: 14362101

[67] Haase, H.J.; Janssen, P.A.L. *The action of neuroleptic drugs: A psychiatric, neurologic, and pharmacological investigation*; North Holland: Netherlands, **1958**.

[68] Hippius, H. The founding of the CINP and the discovery of clozapine.*The Psychopharmacologists*; Healy, D., Ed.; Chapman & Hall: New York, NY, **1996**, pp. 185-213.

[69] Shen, W.W. Pharmacotherapy of schizophrenia: the American current status. *Keio J. Med.,* **1994**, *43*(4), 192-200. http://dx.doi.org/10.2302/kjm.43.192 PMID: 7861689

[70] Hippius, H. The history of clozapine. *Psychopharmacology (Berl.),* **1989**, *99*(Suppl.), S3-S5. http://dx.doi.org/10.1007/BF00442551 PMID: 2682730

[71] Gross, H.; Langner, E. Das Wirkungsprofil eines chemisch neuartigen Breitbandneuroleptikums der Dibenzodiazepingruppe. *Wien. Med. Wochenschr.,* **1966**, *116*(40), 814-816. PMID: 5925777

[72] Bente, D.; Engelmeier, M.P.; Heinrich, K.; Hippius, H.; Schmitt, W. Klinische Untersuchungen mit einem neuroleptisch wirksamen Dibenzothiazepin-Derivat. *Arzneimittelforschung,* **1966**, *16*(2), 314-316. PMID: 4861661

[73] Angst, J.; Jaenicke, U.; Padrutt, A.; Scharfetter, C. Ergebnisse eines doppelblindversuches von HF 1854 (8-Chlor-11-(4-methyl-1-piperazinyl)-5H-dibenzo(b,e)(1,4)diazepin) im vergleich zu levomepromazin. *Pharrnackopsychiatrie,* **1971**, *4*, 192-200. http://dx.doi.org/10.1055/s-0028-1094312

[74] Kane, J.; Honigfeld, G.; Singer, J.; Meltzer, H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch. Gen. Psychiatry,* **1988**, *45*(9), 789-796. http://dx.doi.org/10.1001/archpsyc.1988.01800330013001 PMID: 3046553

[75] Munoz-Bellido, J.L.; Munoz-Criado, S.; Garcìa-Rodrìguez, J.A. Antimicrobial activity of psychotropic drugs: selective serotonin reuptake inhibitors. *Int. J. Antimicrob. Agents,* **2000**, *14*(3), 177-180. http://dx.doi.org/10.1016/S0924-8579(99)00154-5 PMID: 10773485

[76] Macedo, D.; Filho, A.J.M.C.; Soares de Sousa, C.N.; Quevedo, J.; Barichello, T.; Júnior, H.V.N.; Freitas de Lucena, D. Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness. *J. Affect. Disord.,* **2017**, *208*, 22-32. http://dx.doi.org/10.1016/j.jad.2016.09.012 PMID: 27744123

[77] Ordway, D.; Viveiros, M.; Leandro, C.; Bettencourt, R.; Almeida, J.; Martins, M.; Kristiansen, J.E.; Molnar, J.; Amaral, L. Clinical concentrations of thioridazine kill intracellular multidrug-resistant Mycobacterium tuberculosis. *Antimicrob. Agents Chemother.,* **2003**, *47*(3), 917-922. http://dx.doi.org/10.1128/AAC.47.3.917-922.2003 PMID: 12604522

[78] Ordway, D.; Viveiros, M.; Leandro, C.; Arroz, M.J.; Amaral, L. Intracellular activity of clinical concentrations of phenothiazines including thioridiazine against phagocytosed Staphylococcus aureus. *Int. J. Antimicrob. Agents,* **2002**, *20*(1), 34-43. http://dx.doi.org/10.1016/S0924-8579(02)00110-3 PMID: 12127709

[79] Kristiansen, M.M.; Leandro, C.; Ordway, D.; Martins, M.; Viveiros, M.; Pacheco, T.; Kristiansen, J.E.; Amaral, L. Phenothiazines alter resistance of methicillin-resistant strains of Staphylococcus aureus (MRSA) to oxacillin *in vitro*. *Int. J. Antimicrob. Agents,* **2003**, *22*(3), 250-253. http://dx.doi.org/10.1016/S0924-8579(03)00200-0 PMID: 13678829

[80] Amaral, L.; Viveiros, M.; Molnár, J. Antimicrobial activity of phenothiazines. *In Vivo,* **2004**, *18*(6), 725-731. PMID: 15646813

[81] Lieb, J. The immunostimulating and antimicrobial properties of lithium and antidepressants. *J. Infect.,* **2004**, *49*(2), 88-93. http://dx.doi.org/10.1016/j.jinf.2004.03.006 PMID: 15236914

[82] Nehme, H.; Saulnier, P.; Ramadan, A.A.; Cassisa, V.; Guillet, C.; Eveillard, M.; Umerska, A. Antibacterial activity of antipsychotic agents, their association with lipid nanocapsules and its impact on the properties of the nanocarriers and on antibacterial activity. *PLoS One,* **2018**, *13*(1)e0189950 http://dx.doi.org/10.1371/journal.pone.0189950 PMID: 29298353

[83] Li, H.; Li, J.; Yu, X.; Zheng, H.; Sun, X.; Lu, Y.; Zhang, Y.; Li, C.; Bi, X. The incidence rate of cancer in patients with schizophrenia: A meta-analysis of cohort studies. *Schizophr. Res.,* **2018**, *195*, 519-528. http://dx.doi.org/10.1016/j.schres.2017.08.065 PMID: 28943096

[84] Chou, F.H.; Tsai, K.Y.; Su, C.Y.; Lee, C.C. The incidence and relative risk factors for developing cancer among patients with schizophrenia: a nine-year follow-up study. *Schizophr. Res.,* **2011**, *129*(2-3), 97-103. http://dx.doi.org/10.1016/j.schres.2011.02.018 PMID: 21458957

[85] Grinshpoon, A.; Barchana, M.; Ponizovsky, A.; Lipshitz, I.; Nahon, D.; Tal, O.; Weizman, A.; Levav, I. Cancer in schizophrenia: is the risk higher or lower? *Schizophr. Res.,* **2005**, *73*(2-3), 333-341. http://dx.doi.org/10.1016/j.schres.2004.06.016 PMID: 15653279

[86] Barak, Y.; Achiron, A.; Mandel, M.; Mirecki, I.; Aizenberg, D. Reduced cancer incidence among patients with schizophrenia. *Cancer,* **2005**, *104*(12), 2817-2821. http://dx.doi.org/10.1002/cncr.21574 PMID: 16288491

[87] Cohen, M.; Dembling, B.; Schorling, J. The association between schizophrenia and cancer: a population-based mortality study. *Schizophr. Res.,* **2002**, *57*(2-3), 139-146. http://dx.doi.org/10.1016/S0920-9964(01)00308-5 PMID: 12223244

[88] Spengler, G.; Csonka, Á.; Molnár, J.; Amaral, L. The anticancer activity of the old neuroleptic phenothiazine-type drug thioridazine. *Anticancer Res.,* **2016**, *36*(11), 5701-5706. http://dx.doi.org/10.21873/anticanres.11153 PMID: 27793891

[89] Chen, J.J.; Cai, N.; Chen, G.Z.; Jia, C.C.; Qiu, D.B.; Du, C.; Liu, W.; Yang, Y.; Long, Z.J.; Zhang, Q. The neuroleptic drug pimozide inhibits stem-like cell maintenance and tumorigenicity in hepatocellular carcinoma. *Oncotarget,* **2017**, *8*(11), 17593-17609. http://dx.doi.org/10.18632/oncotarget.4307 PMID: 26061710

[90] Duenas-Gonzalez, A.; Candelaria, M.; Perez-Plascencia, C.; Perez-Cardenas, E.; de la Cruz-Hernandez, E.; Herrera, L.A. Valproic acid as epigenetic cancer drug: preclinical, clinical and transcriptional effects on solid tumors. *Cancer Treat. Rev.,* **2008**, *34*(3), 206-222. http://dx.doi.org/10.1016/j.ctrv.2007.11.003 PMID: 18226465

[91] Caruso, R.; Grassi, L.; Nanni, M.G.; Riba, M. Psychopharmacology in psycho-oncology. *Curr. Psychiatry Rep.,* **2013**, *15*(9), 393. http://dx.doi.org/10.1007/s11920-013-0393-0 PMID: 23949568

[92] Thekdi, S.M.; Trinidad, A.; Roth, A. Psychopharmacology in cancer. *Curr. Psychiatry Rep.,* **2015**, *17*(1), 529. http://dx.doi.org/10.1007/s11920-014-0529-x PMID: 25417593

[93] Grassi, L.; Caruso, R.; Hammelef, K.; Nanni, M.G.; Riba, M. Efficacy and safety of pharmacotherapy in cancer-related psychiatric disorders across the trajectory of cancer care: a review. *Int. Rev. Psychiatry,* **2014**, *26*(1), 44-62. http://dx.doi.org/10.3109/09540261.2013.842542 PMID: 24716500

[94] Chang, S.C.; Shen, W.W. Antidepressant therapy in patients with cancer: A clinical review. *Taiwan. J. Psychiatry,* **2019**, *33*, 13-19. http://dx.doi.org/10.4103/TPSY.TPSY_3_19

[95] Bielecka, A.M.; Obuchowicz, E. Antidepressant drugs as a complementary therapeutic strategy in cancer. *Exp. Biol. Med. (Maywood),* **2013**, *238*(8), 849-858. http://dx.doi.org/10.1177/1535370213493721 PMID: 23970405

[96] Cipriani, A.; Purgato, M.; Furukawa, T.A.; Trespidi, C.; Imperadore, G.; Signoretti, A.; Churchill, R.; Watanabe, N.; Barbui, C. Citalopram versus other anti-depressive agents for depression. *Cochrane Database Syst. Rev.,* **2012**, *7*(7)CD006534 http://dx.doi.org/10.1002/14651858.CD006534.pub2 PMID: 22786497

[97] Nemeroff, C.B. Overview of the safety of citalopram. *Psychopharmacol. Bull.,* **2003**, *37*(1), 96-121. PMID: 14561952

[98] Keller, M.B. Citalopram therapy for depression: a review of 10 years of European experience and data from U.S. clinical trials. *J. Clin. Psychiatry,* **2000**, *61*(12), 896-908. http://dx.doi.org/10.4088/JCP.v61n1202 PMID: 11206593

[99] McCarrell, J.L.; Bailey, T.A.; Duncan, N.A.; Covington, L.P.; Clifford, K.M.; Hall, R.G.; Blaszczyk, A.T. A review of citalopram dose restrictions in the treatment of neuropsychiatric disorders in older adults. *Ment Health Clin,* **2019**, *9*(4), 280-286. http://dx.doi.org/10.9740/mhc.2019.07.280 PMID: 31293848

[100] Ahmed, E. Antidepressants in patients with advanced cancer: When they're warranted and how to choose therapy. *Oncology (Williston Park),* **2019**, *33*(2), 62-68. PMID: 30784031

[101] Nguyen, T.; Vallejo, R.; Benyamin, R.; Kramer, J.; Vogel, L.A. A potential role for Citalopram as an immunoenhancer on morphine-induced immunosuppression. *J. Immunol.,* **2007**, *178*, S202.

[102] Xu, W.; Tamim, H.; Shapiro, S.; Stang, M.R.; Collet, J.P. Use of antidepressants and risk of colorectal cancer: a nested case-control study. *Lancet Oncol.,* **2006**, *7*(4), 301-308. http://dx.doi.org/10.1016/S1470-2045(06)70622-2 PMID: 16574545

[103] Coogan, P.F.; Strom, B.L.; Rosenberg, L. Antidepressant use and colorectal cancer risk. *Pharmacoepidemiol. Drug Saf.,* **2009**, *18*(11), 1111-1114. http://dx.doi.org/10.1002/pds.1808 PMID: 19623565

[104] Chubak, J.; Boudreau, D.M.; Rulyak, S.J.; Mandelson, M.T. Colorectal cancer risk in relation to antidepressant medication use. *Int. J. Cancer,* **2011**, *128*(1), 227-232. http://dx.doi.org/10.1002/ijc.25322 PMID: 20232382

[105] Iskar, M.; Bork, P.; van Noort, V. Discovery and validation of the antimetastatic activity of citalopram in colorectal cancer. *Mol. Cell. Oncol.,* **2015**, *2*(2)e975080 http://dx.doi.org/10.4161/23723556.2014.975080 PMID: 27308430

[106] van Noort, V.; Schölch, S.; Iskar, M.; Zeller, G.; Ostertag, K.; Schweitzer, C.; Werner, K.; Weitz, J.; Koch, M.; Bork, P. Novel drug candidates for the treatment of metastatic colorectal cancer through global inverse gene-expression profiling. *Cancer Res.,* **2014**, *74*(20), 5690-5699. http://dx.doi.org/10.1158/0008-5472.CAN-13-3540 PMID: 25038229

[107] Tutton, P.J.; Barkla, D.H. Influence of inhibitors of serotonin uptake on intestinal epithelium and colorectal carcinomas. *Br. J. Cancer,* **1982**, *46*(2), 260-265. http://dx.doi.org/10.1038/bjc.1982.191 PMID: 6983886

[108] Tutton, P.J.; Steel, G.G. Influence of biogenic amines on the growth of xenografted human colorectal carcinomas. *Br. J. Cancer,* **1979**, *40*(5), 743-749. http://dx.doi.org/10.1038/bjc.1979.255 PMID: 41563

[109] Barkla, D.H.; Tutton, P.J. Influence of histamine and serotonin antagonists on the growth of xenografted human colorectal tumors. *J. Natl. Cancer Inst.,* **1981**, *67*(6), 1207-1211. PMID: 6947106

[110] Ahmadian, E.; Eftekhari, A.; Babaei, H.; Nayebi, A.M.; Eghbal, M.A. Anti-cancer effects of citalopram on hepatocellular carcinoma cells occur via cytochrome c release and the activation of NF-κB. *Anticancer. Agents Med. Chem.,* **2017**, *17*(11), 1570-1577. http://dx.doi.org/10.2174/1871520617666170327155930 PMID: 28356024

[111] Chen, V.C.H.; Lin, C.F.; Hsieh, Y.H.; Liang, H.Y.; Huang, K.Y.; Chiu, W.C.; Lee, Y.; McIntyre, R.S.; Chan, H.L. Hepatocellular carcinoma and antidepressants: a nationwide population-based study. *Oncotarget,* **2017**, *8*(18), 30464-30470. http://dx.doi.org/10.18632/oncotarget.12826 PMID: 27783998

[112] Chan, H.L.; Chiu, W.C.; Chen, V.C.H.; Huang, K.Y.; Wang, T.N.; Lee, Y.; McIntyre, R.S.; Hsu, T.C.; Lee, C.T.; Tzang, B.S. SSRIs associated with decreased risk of hepatocellular carcinoma: A population-based case-control study. *Psychooncology,* **2018**, *27*(1), 187-192. http://dx.doi.org/10.1002/pon.4493 PMID: 28666060

[113] Sakka, L.; Delétage, N.; Chalus, M.; Aissouni, Y.; Sylvain-Vidal, V.; Gobron, S.; Coll, G. Assessment of citalopram and escitalopram on neuroblastoma cell lines. Cell toxicity and gene modulation. *Oncotarget,* **2017**, *8*(26), 42789-42807. http://dx.doi.org/10.18632/oncotarget.17050 PMID: 28467792

[114] Louis, C.U.; Shohet, J.M. Neuroblastoma: molecular pathogenesis and therapy. *Annu. Rev. Med.,* **2015**, *66*, 49-63. http://dx.doi.org/10.1146/annurev-med-011514-023121 PMID: 25386934

[115] Xia, Z.; Bergstrand, A.; DePierre, J.W.; Nässberger, L. The antidepressants imipramine, clomipramine, and citalopram induce apoptosis in human acute myeloid leukemia HL-60

cells via caspase-3 activation. *J. Biochem. Mol. Toxicol.,* **1999**, *13*(6), 338-347. http://dx.doi.org/10.1002/(SICI)1099-0461(1999)13:6<338::AID-JBT8>3.0.CO;2-7 PMID: 10487422

[116] Xia, Z.; Lundgren, B.; Bergstrand, A.; DePierre, J.W.; Nässberger, L. Changes in the generation of reactive oxygen species and in mitochondrial membrane potential during apoptosis induced by the antidepressants imipramine, clomipramine, and citalopram and the effects on these changes by Bcl-2 and Bcl-X(L). *Biochem. Pharmacol.,* **1999**, *57*(10), 1199-1208. http://dx.doi.org/10.1016/S0006-2952(99)00009-X PMID: 11230808

[117] Liou, G.Y.; Storz, P. Reactive oxygen species in cancer. *Free Radic. Res.,* **2010**, *44*(5), 479-496. http://dx.doi.org/10.3109/10715761003667554 PMID: 20370557

[118] Serafeim, A.; Holder, M.J.; Grafton, G.; Chamba, A.; Drayson, M.T.; Luong, Q.T.; Bunce, C.M.; Gregory, C.D.; Barnes, N.M.; Gordon, J. Selective serotonin reuptake inhibitors directly signal for apoptosis in biopsy-like Burkitt lymphoma cells. *Blood,* **2003**, *101*(8), 3212-3219. http://dx.doi.org/10.1182/blood-2002-07-2044 PMID: 12515726

[119] Kabolizadeh, P.; Engelmann, B.J.; Pullen, N.; Stewart, J.K.; Ryan, J.J.; Farrell, N.P. Platinum anticancer agents and antidepressants: desipramine enhances platinum-based cytotoxicity in human colon cancer cells. *J. Biol. Inorg. Chem.,* **2012**, *17*(1), 123-132. http://dx.doi.org/10.1007/s00775-011-0836-1 PMID: 21918844

[120] Engelmann, B.J.; Ryan, J.J.; Farrell, N.P. Antidepressants and platinum drugs. *Anticancer Res.,* **2014**, *34*(1), 509-516. PMID: 24403509

[121] Sommi, R.W.; Crismon, M.L.; Bowden, C.L. Fluoxetine: a serotonin-specific, second-generation antidepressant. *Pharmacotherapy,* **1987**, *7*(1), 1-15. http://dx.doi.org/10.1002/j.1875-9114.1987.tb03496.x PMID: 3554156

[122] Rossi, A.; Barraco, A.; Donda, P. Fluoxetine: a review on evidence based medicine. *Ann. Gen. Hosp. Psychiatry,* **2004**, *3*(1), 2. http://dx.doi.org/10.1186/1475-2832-3-2 PMID: 14962351

[123] Wenthur, C.J.; Bennett, M.R.; Lindsley, C.W. Classics in chemical neuroscience: Fluoxetine (Prozac). *ACS Chem. Neurosci.,* **2014**, *5*, 14-23. http://dx.doi.org/10.1021/cn400186j

[124] Ferguson, J.M. SSRI antidepressant medications: Adverse effects and tolerability. *Prim. Care Companion J. Clin. Psychiatry,* **2001**, *3*(1), 22-27. http://dx.doi.org/10.4088/PCC.v03n0105 PMID: 15014625

[125] The Guardian – Social Care. https://www.theguardian.com/society/2007/may/13/socialcare.medicineandhealth2020 [(Access ed April 03, 2020).];

[126] Nishida, N.; Yano, H.; Nishida, T.; Kamura, T.; Kojiro, M. Angiogenesis in cancer. *Vasc. Health Risk Manag.,* **2006**, *2*(3), 213-219. http://dx.doi.org/10.2147/vhrm.2006.2.3.213 PMID: 17326328

[127] Guba, M.; Yezhelyev, M.; Eichhorn, M.E.; Schmid, G.; Ischenko, I.; Papyan, A.; Graeb, C.; Seeliger, H.; Geissler, E.K.; Jauch, K.W.; Bruns, C.J. Rapamycin induces tumor-specific thrombosis via tissue factor in the presence of VEGF. *Blood,* **2005**, *105*(11), 4463-4469. http://dx.doi.org/10.1182/blood-2004-09-3540 PMID: 15671443

[128] Kannen, V.; Hintzsche, H.; Zanette, D.L.; Silva, W.A., Jr; Garcia, S.B.; Waaga-Gasser, A.M.; Stopper, H. Antiproliferative effects of fluoxetine on colon cancer cells and in a colonic carcinogen mouse model. *PLoS One,* **2012**, *7*(11)e50043 http://dx.doi.org/10.1371/journal.pone.0050043 PMID: 23209640

[129] Kannen, V.; Marini, T.; Turatti, A.; Carvalho, M.C.; Brandão, M.L.; Jabor, V.A.; Bonato, P.S.; Ferreira, F.R.; Zanette, D.L.; Silva, W.A., Jr; Garcia, S.B. Fluoxetine induces preventive and complex effects against colon cancer development in epithelial and stromal areas in rats. *Toxicol. Lett.,* **2011**, *204*(2-3), 134-140. http://dx.doi.org/10.1016/j.toxlet.2011.04.024 PMID: 21554931

[130] Kannen, V.; Garcia, S.B.; Silva, W.A., Jr; Gasser, M.; Mönch, R.; Alho, E.J.; Heinsen, H.; Scholz, C.J.; Friedrich, M.; Heinze, K.G.; Waaga-Gasser, A.M.; Stopper, H. Oncostatic effects of fluoxetine in experimental colon cancer models. *Cell. Signal.,* **2015**, *27*(9), 1781-1788. http://dx.doi.org/10.1016/j.cellsig.2015.05.008 PMID: 26004136

[131] Bai, J.; Li, Y.; Zhang, G. Cell cycle regulation and anticancer drug discovery. *Cancer Biol. Med.,* **2017**, *14*(4), 348-362. http://dx.doi.org/10.20892/j.issn.2095-3941.2017.0033 PMID: 29372101

[132] Vazquez, A.; Bond, E.E.; Levine, A.J.; Bond, G.L. The genetics of the p53 pathway, apoptosis and cancer therapy. *Nat. Rev. Drug Discov.,* **2008**, *7*(12), 979-987. http://dx.doi.org/10.1038/nrd2656 PMID: 19043449

[133] Stepulak, A.; Rzeski, W.; Sifringer, M.; Brocke, K.; Gratopp, A.; Kupisz, K.; Turski, L.; Ikonomidou, C. Fluoxetine inhibits the extracellular signal regulated kinase pathway and suppresses growth of cancer cells. *Cancer Biol. Ther.,* **2008**, *7*(10), 1685-1693. http://dx.doi.org/10.4161/cbt.7.10.6664 PMID: 18836303

[134] Marcinkute, M.; Afshinjavid, S.; Fatokun, A.A.; Javid, F.A. Fluoxetine selectively induces p53-independent apoptosis in human colorectal cancer cells. *Eur. J. Pharmacol.,* **2019**, *857*172441 http://dx.doi.org/10.1016/j.ejphar.2019.172441 PMID: 31181210

[135] Mun, A.R.; Lee, S.J.; Kim, G.B.; Kang, H.S.; Kim, J.S.; Kim, S.J. Fluoxetine-induced apoptosis in hepatocellular carcinoma cells. *Anticancer Res.,* **2013**, *33*(9), 3691-3697. PMID: 24023297

[136] Hsu, L.C.; Tu, H.F.; Hsu, F.T.; Yueh, P.F.; Chiang, I.T. Beneficial effect of fluoxetine on anti-tumor progression on hepatocellular carcinoma and non-small cell lung cancer bearing animal model. *Biomed. Pharmacother.,* **2020**, *126*110054 http://dx.doi.org/10.1016/j.biopha.2020.110054 PMID: 32145588

[137] Kirkova, M.; Tzvetanova, E.; Vircheva, S.; Zamfirova, R.; Grygier, B.; Kubera, M. Antioxidant activity of fluoxetine: studies in mice melanoma model. *Cell Biochem. Funct.,* **2010**, *28*(6), 497-502. http://dx.doi.org/10.1002/cbf.1682 PMID: 20803706

[138] Qi, H.; Ma, J.; Liu, Y.M.; Yang, L.; Peng, L.; Wang, H.; Chen, H.Z. Allostatic tumor-burden induces depression-associated changes in hepatoma-bearing mice. *J. Neurooncol.,* **2009**, *94*(3), 367-372.

http://dx.doi.org/10.1007/s11060-009-9887-3 PMID: 19381448

[139] Lee, C.S.; Kim, Y.J.; Jang, E.R.; Kim, W.; Myung, S.C. Fluoxetine induces apoptosis in ovarian carcinoma cell line OVCAR-3 through reactive oxygen species-dependent activation of nuclear factor-kappaB. *Basic Clin. Pharmacol. Toxicol.,* **2010**, *106*(6), 446-453. http://dx.doi.org/10.1111/j.1742-7843.2009.00509.x PMID: 20050848

[140] Ereshefsky, L.; Riesenman, C.; Lam, Y.W. Antidepressant drug interactions and the cytochrome P450 system. The role of cytochrome P450 2D6. *Clin. Pharmacokinet.,* **1995**, *29*(Suppl. 1), 10-18. http://dx.doi.org/10.2165/00003088-199500291-00004 PMID: 8846618

[141] Weiner, S.A.; Alberts, D.S.; Surwit, E.A.; Davis, J.; Grosso, D. Tamoxifen therapy in recurrent epithelial ovarian carcinoma. *Gynecol. Oncol.,* **1987**, *27*(2), 208-213. http://dx.doi.org/10.1016/0090-8258(87)90294-0 PMID: 3570058

[142] Markman, M.; Iseminger, K.A.; Hatch, K.D.; Creasman, W.T.; Barnes, W.; Dubeshter, B. Tamoxifen in platinum-refractory ovarian cancer: a Gynecologic Oncology Group Ancillary Report. *Gynecol. Oncol.,* **1996**, *62*(1), 4-6. http://dx.doi.org/10.1006/gyno.1996.0181 PMID: 8690289

[143] Sukasem, C.; Sirachainan, E.; Chamnanphon, M.; Pechatanan, K.; Sirisinha, T.; Ativitavas, T.; Panvichian, R.; Ratanatharathorn, V.; Trachu, N.; Chantratita, W. Impact of CYP2D6 polymorphisms on tamoxifen responses of women with breast cancer: a microarray-based study in Thailand. *Asian Pac. J. Cancer Prev.,* **2012**, *13*(9), 4549-4553. http://dx.doi.org/10.7314/APJCP.2012.13.9.4549 PMID: 23167378

[144] Christensen, D.K.; Armaiz-Pena, G.N.; Ramirez, E.; Matsuo, K.; Zimmerman, B.; Zand, B.; Shinn, E.; Goodheart, M.J.; Bender, D.; Thaker, P.H.; Ahmed, A.; Penedo, F.J.; DeGeest, K.; Mendez, L.; Domann, F.; Sood, A.K.; Lutgendorf, S.K. SSRI use and clinical outcomes in epithelial ovarian cancer. *Oncotarget,* **2016**, *7*(22), 33179-33191. http://dx.doi.org/10.18632/oncotarget.8891 PMID: 27121207

[145] Brandes, L.J.; Arron, R.J.; Bogdanovic, R.P.; Tong, J.; Zaborniak, C.L.; Hogg, G.R.; Warrington, R.C.; Fang, W.; LaBella, F.S. Stimulation of malignant growth in rodents by antidepressant drugs at clinically relevant doses. *Cancer Res.,* **1992**, *52*(13), 3796-3800. PMID: 1617649

[146] Steingart, A.; Cotterchio, M.; Kreiger, N.; Sloan, M. Antidepressant medication use and breast cancer risk: a case-control study. *Int. J. Epidemiol.,* **2003**, *32*(6), 961-966. http://dx.doi.org/10.1093/ije/dyg155 PMID: 14681256

[147] Cloonan, S.M.; Williams, D.C. The antidepressants maprotiline and fluoxetine induce Type II autophagic cell death in drug-resistant Burkitt's lymphoma. *Int. J. Cancer,* **2011**, *128*(7), 1712-1723. http://dx.doi.org/10.1002/ijc.25477 PMID: 20503272

[148] Abdul, M.; Logothetis, C.J.; Hoosein, N.M. Growth-inhibitory effects of serotonin uptake inhibitors on human prostate carcinoma cell lines. *J. Urol.,* **1995**, *154*(1), 247-250. http://dx.doi.org/10.1016/S0022-5347(01)67288-4 PMID: 7776439

[149] Bowie, M.; Pilie, P.; Wulfkuhle, J.; Lem, S.; Hoffman, A.; Desai, S.; Petricoin, E.; Carter, A.; Ambrose, A.; Seewaldt, V.; Yu, D.; Ibarra Drendall, C. Fluoxetine induces cytotoxic endoplasmic reticulum stress and autophagy in triple negative breast cancer. *World J. Clin. Oncol.,* **2015**, *6*(6), 299-311. http://dx.doi.org/10.5306/wjco.v6.i6.299 PMID: 26677444

[150] Levkovitz, Y.; Gil-Ad, I.; Zeldich, E.; Dayag, M.; Weizman, A. Differential induction of apoptosis by antidepressants in glioma and neuroblastoma cell lines: evidence for p-c-Jun, cytochrome c, and caspase-3 involvement. *J. Mol. Neurosci.,* **2005**, *27*(1), 29-42. http://dx.doi.org/10.1385/JMN:27:1:029 PMID: 16055945

[151] Choi, J.H.; Jeong, Y.J.; Yu, A.R.; Yoon, K.S.; Choe, W.; Ha, J.; Kim, S.S.; Yeo, E.J.; Kang, I. Fluoxetine induces apoptosis through endoplasmic reticulum stress via mitogen-activated protein kinase activation and histone hyperacetylation in SK-N-BE(2)-M17 human neuroblastoma cells. *Apoptosis,* **2017**, *22*(9), 1079-1097. http://dx.doi.org/10.1007/s10495-017-1390-2 PMID: 28647884

[152] Liu, Y.; Li, T.; Xu, M.; Che, X.; Jiang, X. Fluoxetine enhances cellular chemosensitivity to cisplatin in cervical cancer. *Int. J. Clin. Exp. Med.,* **2017**, *10*, 10521-10527.

[153] Pae, C.U.; Patkar, A.A. Paroxetine: current status in psychiatry. *Expert Rev. Neurother.,* **2007**, *7*(2), 107-120. http://dx.doi.org/10.1586/14737175.7.2.107 PMID: 17286545

[154] Grimsley, S.R.; Jann, M.W. Paroxetine, sertraline, and fluvoxamine: new selective serotonin reuptake inhibitors. *Clin. Pharm.,* **1992**, *11*(11), 930-957. PMID: 1464219

[155] Johnson, A.M. Paroxetine: a pharmacological review. *Int. Clin. Psychopharmacol.,* **1992**, *6*(Suppl. 4), 15-24. http://dx.doi.org/10.1097/00004850-199206004-00005 PMID: 1331230

[156] Foster, R.H.; Goa, K.L. Paroxetine : a review of its pharmacology and therapeutic potential in the management of panic disorder. *CNS Drugs,* **1997**, *8*(2), 163-188. http://dx.doi.org/10.2165/00023210-199708020-00010 PMID: 23338224

[157] Sanchez, C.; Reines, E.H.; Montgomery, S.A. A comparative review of escitalopram, paroxetine, and sertraline: Are they all alike? *Int. Clin. Psychopharmacol.,* **2014**, *29*(4), 185-196. http://dx.doi.org/10.1097/YIC.0000000000000023 PMID: 24424469

[158] Nevels, R.M.; Gontkovsky, S.T.; Williams, B.E. Paroxetine – The antidepressant from hell? Probably not, but caution required. *Psychopharmacol. Bull.,* **2016**, *46*(1), 77-104. PMID: 27738376

[159] Purgato, M.; Papola, D.; Gastaldon, C.; Trespidi, C.; Magni, L.R.; Rizzo, C.; Furukawa, T.A.; Watanabe, N.; Cipriani, A.; Barbui, C. Paroxetine versus other anti-depressive agents for depression. *Cochrane Database Syst. Rev.,* **2014**, *4*(4)CD006531 http://dx.doi.org/10.1002/14651858.CD006531.pub2 PMID: 24696195

[160] Gil-Ad, I.; Zolokov, A.; Lomnitski, L.; Taler, M.; Bar, M.; Luria, D.; Ram, E.; Weizman, A. Evaluation of the potential anti-cancer activity of the antidepressant sertraline in human colon cancer cell lines and in colorectal cancer-xenografted mice. *Int. J. Oncol.,* **2008**, *33*(2), 277-286. PMID: 18636148

[161] Jang, W.J.; Jung, S.K.; Vo, T.T.L.; Jeong, C.H. Anticancer activity of paroxetine in human colon cancer cells: Involvement of MET and ERBB3. *J. Cell. Mol. Med.,* **2019**, *23*(2), 1106-1115. http://dx.doi.org/10.1111/jcmm.14011 PMID: 30421568

[162] Shibuya, T. Paroxetine, a selective serotonin re-uptake inhibitor, induces growth inhibition and apoptosis in prostate cancer cells. *Cancer Res.,* **2011**, *71*, 2152.

[163] Pan, C.C.; Kuo, D.H.; Shieh, P.; Chen, F.A.; Kuo, C.C.; Jan, C.R. Effect of the antidepressant paroxetine on Ca2+ movement in PC3 human prostate cancer cells. *Drug Dev. Res.,* **2010**, *71*, 120-126. http://dx.doi.org/10.1002/ddr.20377

[164] Cho, Y.W.; Kim, E.J.; Nyiramana, M.M.; Shin, E.J.; Jin, H.; Ryu, J.H.; Kang, K.R.; Lee, G.W.; Kim, H.J.; Han, J.; Kang, D. Paroxetine induces apoptosis of human breast cancer MCF-7 cells through Ca2+ and p38 MAP kinase-dependent ROS generation. *Cancers (Basel),* **2019**, *11*(1), 64. http://dx.doi.org/10.3390/cancers11010064 PMID: 30634506

[165] Fang, Y.C.; Chou, C.T.; Pan, C.C.; Hsieh, Y.D.; Liang, W.Z.; Chao, D.; Tsai, J.Y.; Liao, W.C.; Kuo, D.H.; Shieh, P.; Kuo, C.C.; Jan, C.R.; Shaw, C.F. Paroxetine-induced Ca2+ movement and death in OC2 human oral cancer cells. *Chin. J. Physiol.,* **2011**, *54*(5), 310-317. PMID: 22135909

[166] Chou, C.T.; He, S.; Jan, C.R. Paroxetine-induced apoptosis in human osteosarcoma cells: activation of p38 MAP kinase and caspase-3 pathways without involvement of [Ca2+]i elevation. *Toxicol. Appl. Pharmacol.,* **2007**, *218*(3), 265-273. http://dx.doi.org/10.1016/j.taap.2006.11.012 PMID: 17174998

[167] Muijsers, R.B.; Plosker, G.L.; Noble, S. Sertraline: a review of its use in the management of major depressive disorder in elderly patients. *Drugs Aging,* **2002**, *19*(5), 377-392. http://dx.doi.org/10.2165/00002512-200219050-00006 PMID: 12093324

[168] McRae, A.L.; Brady, K.T. Review of sertraline and its clinical applications in psychiatric disorders. *Expert Opin. Pharmacother.,* **2001**, *2*(5), 883-892. http://dx.doi.org/10.1517/14656566.2.5.883 PMID: 11336629

[169] Richelson, E. Pharmacology of antidepressants. *Mayo Clin. Proc.,* **2001**, *76*(5), 511-527. http://dx.doi.org/10.4065/76.5.511 PMID: 11357798

[170] Cipriani, A.; La Ferla, T.; Furukawa, T.A.; Signoretti, A.; Nakagawa, A.; Churchill, R.; McGuire, H.; Barbui, C. Sertraline versus other antidepressive agents for depression. *Cochrane Database Syst. Rev.,* **2009**, *2*(2)CD006117 http://dx.doi.org/10.1002/14651858.CD006117.pub2 PMID: 19370626

[171] Chen, S.; Xuan, J.; Wan, L.; Lin, H.; Couch, L.; Mei, N.; Dobrovolsky, V.N.; Guo, L. Sertraline, an antidepressant, induces apoptosis in hepatic cells through the mitogen-activated protein kinase pathway. *Toxicol. Sci.,* **2014**, *137*(2), 404-415. http://dx.doi.org/10.1093/toxsci/kft254 PMID: 24194395

[172] Unterecker, S.; Riederer, P.; Proft, F.; Maloney, J.; Deckert, J.; Pfuhlmann, B. Effects of gender and age on serum concentrations of antidepressants under naturalistic conditions. *J. Neural Transm. (Vienna),* **2013**, *120*(8), 1237-1246. http://dx.doi.org/10.1007/s00702-012-0952-2 PMID: 23254926

[173] Yasui-Furukori, N.; Tsuchimine, S.; Nakagami, T.; Fujii, A.; Sato, Y.; Tomita, T.; Yoshizawa, K.; Inoue, Y.; Kaneko, S. Association between plasma paroxetine concentration and changes in plasma brain-derived neurotrophic factor levels in patients with major depressive disorder. *Hum. Psychopharmacol.,* **2011**, *26*(3), 194-200. http://dx.doi.org/10.1002/hup.1192 PMID: 21638327

[174] Kuwahara, J.; Yamada, T.; Egashira, N.; Ueda, M.; Zukeyama, N.; Ushio, S.; Masuda, S. Comparison of the antitumor effects of selective serotonin reuptake inhibitors as well as serotonin and norepinephrine reuptake inhibitors in human hepatocellular carcinoma cells. *Biol. Pharm. Bull.,* **2015**, *38*(9), 1410-1414. http://dx.doi.org/10.1248/bpb.b15-00128 PMID: 26328498

[175] Elmore, S. Apoptosis: a review of programmed cell death. *Toxicol. Pathol.,* **2007**, *35*(4), 495-516. http://dx.doi.org/10.1080/01926230701320337 PMID: 17562483

[176] Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell,* **2011**, *144*(5), 646-674. http://dx.doi.org/10.1016/j.cell.2011.02.013 PMID: 21376230

[177] Kasap, C.; Elemento, O.; Kapoor, T.M. DrugTargetSeqR: a genomics- and CRISPR-Cas9-based method to analyze drug targets. *Nat. Chem. Biol.,* **2014**, *10*(8), 626-628. http://dx.doi.org/10.1038/nchembio.1551 PMID: 24929528

[178] Levine, B.; Jenkins, A.J.; Smialek, J.E. Distribution of sertraline in postmortem cases. *J. Anal. Toxicol.,* **1994**, *18*(5), 272-274. http://dx.doi.org/10.1093/jat/18.5.272 PMID: 7990446

[179] Lewis, R.J.; Angier, M.K.; Williamson, K.S.; Johnson, R.D. Analysis of sertraline in postmortem fluids and tissues in 11 aviation accident victims. *J. Anal. Toxicol.,* **2013**, *37*(4), 208-216. http://dx.doi.org/10.1093/jat/bkt014 PMID: 23511306

[180] Johansen, L.M.; DeWald, L.E.; Shoemaker, C.J.; Hoffstrom, B.G.; Lear-Rooney, C.M.; Stossel, A.; Nelson, E.; Delos, S.E.; Simmons, J.A.; Grenier, J.M.; Pierce, L.T.; Pajouhesh, H.; Lehár, J.; Hensley, L.E.; Glass, P.J.; White, J.M.; Olinger, G.G. A screen of approved drugs and molecular probes identifies therapeutics with anti-Ebola virus activity. *Sci. Transl. Med.,* **2015**, *7*(290)290ra89 http://dx.doi.org/10.1126/scitranslmed.aaa5597 PMID: 26041706

[181] Juurlink, D. Revisiting the drug interaction between tamoxifen and SSRI antidepressants. *BMJ,* **2016**, *354*, i5309. http://dx.doi.org/10.1136/bmj.i5309 PMID: 27694573

[182] Lin, C.J.; Robert, F.; Sukarieh, R.; Michnick, S.; Pelletier, J. The antidepressant sertraline inhibits translation initiation by curtailing mammalian target of rapamycin signaling. *Cancer Res.,* **2010**, *70*(8), 3199-3208. http://dx.doi.org/10.1158/0008-5472.CAN-09-4072 PMID: 20354178

[183] Bavadekar, S.; Panchal, P.; Hanbashi, A.; Vansal, S. Cytotoxic effects of selective serotonin- and serotonin-norepinephrine reuptake inhibitors on human metastatic breast cancer cell line, MCF-7 (842.3). *FASEB,* **2014**, *28*, 1.

[184] Tzadok, S.; Beery, E.; Israeli, M.; Uziel, O.; Lahav, M.; Fenig, E.; Gil-Ad, I.; Weizman, A.; Nordenberg, J. *In vitro* novel combinations of psychotropics and anti-cancer modalities in U87 human glioblastoma cells. *Int. J. Oncol.,* **2010**, *37*(4), 1043-1051. PMID: 20811727

[185] Amit, B.H.; Gil-Ad, I.; Taler, M.; Bar, M.; Zolokov, A.; Weizman, A. Proapoptotic and chemosensitizing effects of selective serotonin reuptake inhibitors on T cell lymphoma/leukemia (Jurkat) *in vitro*. *Eur. Neuropsychopharmacol.,* **2009**, *19*(10), 726-734. http://dx.doi.org/10.1016/j.euroneuro.2009.06.003 PMID: 19631512

[186] Boia-Ferreira, M.; Basílio, A.B.; Hamasaki, A.E.; Matsubara, F.H.; Appel, M.H.; Da Costa, C.R.V.; Amson, R.; Tel-

erman, A.; Chaim, O.M.; Veiga, S.S.; Senff-Ribeiro, A. TCTP as a therapeutic target in melanoma treatment. *Br. J. Cancer,* **2017**, *117*(5), 656-665.
http://dx.doi.org/10.1038/bjc.2017.230 PMID: 28751755

[187] Reddy, K.K.; Lefkove, B.; Chen, L.B.; Govindarajan, B.; Carracedo, A.; Velasco, G.; Carrillo, C.O.; Bhandarkar, S.S.; Owens, M.J.; Mechta-Grigoriou, F.; Arbiser, J.L. The antidepressant sertraline downregulates Akt and has activity against melanoma cells. *Pigment Cell Melanoma Res.,* **2008**, *21*(4), 451-456.
http://dx.doi.org/10.1111/j.1755-148X.2008.00481.x PMID: 18710373

[188] Chien, J.M.; Chou, C.T.; Pan, C.C.; Kuo, C.C.; Tsai, J.Y.; Liao, W.C.; Kuo, D.H.; Shieh, P.; Ho, C.M.; Chu, S.T.; Su, H.H.; Chi, C.C.; Jan, C.R. The mechanism of sertraline-induced [Ca2+]i rise in human OC2 oral cancer cells. *Hum. Exp. Toxicol.,* **2011**, *30*(10), 1635-1643.
http://dx.doi.org/10.1177/0960327110396523 PMID: 21247994

[189] Drinberg, V.; Bitcover, R.; Rajchenbach, W.; Peer, D. Modulating cancer multidrug resistance by sertraline in combination with a nanomedicine. *Cancer Lett.,* **2014**, *354*(2), 290-298.
http://dx.doi.org/10.1016/j.canlet.2014.08.026 PMID: 25173796

[190] Huang, J.K.; Chang, H.T.; Chou, C.T.; Shu, S.S.; Kuo, C.C.; Tsai, J.Y.; Liao, W.C.; Wang, J.L.; Lin, K.L.; Lu, Y.C.; Chen, I.S.; Liu, S.I.; Ho, C.M.; Jan, C.R. The mechanism of sertraline-induced [Ca(2+)](i) rise in human PC3 prostate cancer cells. *Basic Clin. Pharmacol. Toxicol.,* **2011**, *109*(2), 103-110.
http://dx.doi.org/10.1111/j.1742-7843.2011.00690.x PMID: 21371263

[191] Saha, K.B.; Bo, L.; Zhao, S.; Xia, J.; Sampson, S.; Zaman, R.U. Chlorpromazine versus atypical antipsychotic drugs for schizophrenia. *Cochrane Database Syst. Rev.,* **2016**, *4*CD010631
http://dx.doi.org/10.1002/14651858.CD010631.pub2 PMID: 27045703

[192] López-Muñoz, F.; Alamo, C.; Cuenca, E.; Shen, W.W.; Clervoy, P.; Rubio, G. History of the discovery and clinical introduction of chlorpromazine. *Ann. Clin. Psychiatry,* **2005**, *17*(3), 113-135.
http://dx.doi.org/10.1080/10401230591002002 PMID: 16433053

[193] Dudley, K.; Liu, X.; De Haan, S. Chlorpromazine dose for people with schizophrenia. *Cochrane Database Syst. Rev.,* **2017**, *4*CD007778
PMID: 28407198

[194] Leucht, C.; Kitzmantel, M.; Chua, L.; Kane, J.; Leucht, S. Haloperidol versus chlorpromazine for schizophrenia. *Cochrane Database Syst. Rev.,* **2008**, *1*(1)CD004278
PMID: 18254045

[195] Baumeister, A.A. The chlorpromazine enigma. *J. Hist. Neurosci.,* **2013**, *22*(1), 14-29.
http://dx.doi.org/10.1080/0964704X.2012.664087 PMID: 23323529

[196] Howanitz, E.; Pardo, M.; Smelson, D.A.; Engelhart, C.; Eisenstein, N.; Stern, R.G.; Losonczy, M.F. The efficacy and safety of clozapine versus chlorpromazine in geriatric schizophrenia. *J. Clin. Psychiatry,* **1999**, *60*(1), 41-44.
http://dx.doi.org/10.4088/JCP.v60n0109 PMID: 10074877

[197] Shin, S.Y.; Kim, C.G.; Kim, S.H.; Kim, Y.S.; Lim, Y.; Lee, Y.H. Chlorpromazine activates p21Waf1/Cip1 gene transcription via early growth response-1 (Egr-1) in C6 glioma cells. *Exp. Mol. Med.,* **2010**, *42*(5), 395-405.
http://dx.doi.org/10.3858/emm.2010.42.5.041 PMID: 20368687

[198] Shin, S.Y.; Lee, K.S.; Choi, Y.K.; Lim, H.J.; Lee, H.G.; Lim, Y.; Lee, Y.H. The antipsychotic agent chlorpromazine induces autophagic cell death by inhibiting the Akt/mTOR pathway in human U-87MG glioma cells. *Carcinogenesis,* **2013**, *34*(9), 2080-2089.
http://dx.doi.org/10.1093/carcin/bgt169 PMID: 23689352

[199] Oliva, C.R.; Zhang, W.; Langford, C.; Suto, M.J.; Griguer, C.E. Repositioning chlorpromazine for treating chemoresistant glioma through the inhibition of cytochrome c oxidase bearing the COX4-1 regulatory subunit. *Oncotarget,* **2017**, *8*(23), 37568-37583.
http://dx.doi.org/10.18632/oncotarget.17247 PMID: 28455961

[200] Chen, M.H.; Yang, W.L.; Lin, K.T.; Liu, C.H.; Liu, Y.W.; Huang, K.W.; Chang, P.M.; Lai, J.M.; Hsu, C.N.; Chao, K.M.; Kao, C.Y.; Huang, C.Y. Gene expression-based chemical genomics identifies potential therapeutic drugs in hepatocellular carcinoma. *PLoS One,* **2011**, *6*(11)e27186
http://dx.doi.org/10.1371/journal.pone.0027186 PMID: 22087264

[201] Lamb, J.; Crawford, E.D.; Peck, D.; Modell, J.W.; Blat, I.C.; Wrobel, M.J.; Lerner, J.; Brunet, J.P.; Subramanian, A.; Ross, K.N.; Reich, M.; Hieronymus, H.; Wei, G.; Armstrong, S.A.; Haggarty, S.J.; Clemons, P.A.; Wei, R.; Carr, S.A.; Lander, E.S.; Golub, T.R. The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science,* **2006**, *313*(5795), 1929-1935.
http://dx.doi.org/10.1126/science.1132939 PMID: 17008526

[202] Wiklund, E.D.; Catts, V.S.; Catts, S.V.; Ng, T.F.; Whitaker, N.J.; Brown, A.J.; Lutze-Mann, L.H. Cytotoxic effects of antipsychotic drugs implicate cholesterol homeostasis as a novel chemotherapeutic target. *Int. J. Cancer,* **2010**, *126*(1), 28-40.
http://dx.doi.org/10.1002/ijc.24813 PMID: 19662652

[203] Yde, C.W.; Clausen, M.P.; Bennetzen, M.V.; Lykkesfeldt, A.E.; Mouritsen, O.G.; Guerra, B. The antipsychotic drug chlorpromazine enhances the cytotoxic effect of tamoxifen in tamoxifen-sensitive and tamoxifen-resistant human breast cancer cells. *Anticancer Drugs,* **2009**, *20*(8), 723-735.
http://dx.doi.org/10.1097/CAD.0b013e32832ec041 PMID: 19584708

[204] Van Woert, M.H.; Palmer, S.H. Inhibition of the growth of mouse melanoma by chlorpromazine. *Cancer Res.,* **1969**, *29*(11), 1952-1955.
PMID: 4982549

[205] Jones, G.R.N.; Frohn, M.J.N. An injurious effect of chlorpromazine in the murine S180 sarcoma (var. CB) and its relevance to cancer treatment. *Biochem. Soc. Trans.,* **1984**, *12*, 679-680.
http://dx.doi.org/10.1042/bst0120679

[206] Akiyama, S.; Shiraishi, N.; Kuratomi, Y.; Nakagawa, M.; Kuwano, M. Circumvention of multiple-drug resistance in human cancer cells by thioridazine, trifluoperazine, and chlorpromazine. *J. Natl. Cancer Inst.,* **1986**, *76*(5), 839-844.
PMID: 3457971

[207] Lialiaris, T.S.; Papachristou, F.; Mourelatos, C.; Simopoulou, M. Antineoplastic and cytogenetic effects of chlorpromazine on human lymphocytes *in vitro* and on Ehrlich ascites tumor cells *in vivo*. *Anticancer Drugs,* **2009**, *20*(8), 746-751.
http://dx.doi.org/10.1097/CAD.0b013e32832f567b PMID: 19584706

[208] Hait, W.N.; Lazo, J.S.; Chen, D.L.; Gallichio, V.S.; Filderman, A.E. Antitumor and toxic effects of combination che-

motherapy with bleomycin and a phenothiazine anti-calmodulin agent. *J. Natl. Cancer Inst.,* **1988**, *80*(4), 246-250.
http://dx.doi.org/10.1093/jnci/80.4.246 PMID: 2451030

[209] Lee, M.S.; Johansen, L.; Zhang, Y.; Wilson, A.; Keegan, M.; Avery, W.; Elliott, P.; Borisy, A.A.; Keith, C.T. The novel combination of chlorpromazine and pentamidine exerts synergistic antiproliferative effects through dual mitotic action. *Cancer Res.,* **2007**, *67*(23), 11359-11367.
http://dx.doi.org/10.1158/0008-5472.CAN-07-2235 PMID: 18056463

[210] Pinder, R.M.; Brogden, R.N.; Swayer, R.; Speight, T.M.; Spencer, R.; Avery, G.S. Pimozide: a review of its pharmacological properties and therapeutic uses in psychiatry. *Drugs,* **1976**, *12*(1), 1-40.
http://dx.doi.org/10.2165/00003495-197612010-00001 PMID: 824116

[211] Tueth, M.J.; Cheong, J.A. Clinical uses of pimozide. *South. Med. J.,* **1993**, *86*(3), 344-349.
http://dx.doi.org/10.1097/00007611-199303000-00019 PMID: 8451677

[212] Naguy, A. Pimozide: An Old Wine in a New Bottle! *Indian J. Psychol. Med.,* **2017**, *39*(3), 382-383.
http://dx.doi.org/10.4103/IJPSYM.IJPSYM_400_16 PMID: 28615787

[213] Gonçalves, J.M.; Silva, C.A.B.; Rivero, E.R.C.; Cordeiro, M.M.R. Inhibition of cancer stem cells promoted by Pimozide. *Clin. Exp. Pharmacol. Physiol.,* **2019**, *46*(2), 116-125.
http://dx.doi.org/10.1111/1440-1681.13049 PMID: 30383889

[214] Dakir, E.H.; Pickard, A.; Srivastava, K.; McCrudden, C.M.; Gross, S.R.; Lloyd, S.; Zhang, S.D.; Margariti, A.; Morgan, R.; Rudland, P.S.; El-Tanani, M. The anti-psychotic drug pimozide is a novel chemotherapeutic for breast cancer. *Oncotarget,* **2018**, *9*(79), 34889-34910.
http://dx.doi.org/10.18632/oncotarget.26175 PMID: 30405882

[215] Shaw, V.; Srivastava, S.; Srivastava, S.K. Repurposing antipsychotics of the diphenylbutylpiperidine class for cancer therapy. *Semin. Cancer Biol.,* **2019**, 30144-0.
http://dx.doi.org/10.1016/j.semcancer.2019.10.007

[216] Weissenrieder, J.S.; Reed, J.L.; Green, M.V.; Moldovan, G.L.; Koubek, E.J.; Neighbors, J.D.; Hohl, R.J. The dopamine D2 receptor contributes to the spheroid formation behavior of U87 glioblastoma cells. *Pharmacology,* **2020**, *105*(1-2), 19-27.
http://dx.doi.org/10.1159/000502562 PMID: 31645049

[217] Xu, X.; Li, S.; Cui, X.; Han, K.; Wang, J.; Hou, X.; Cui, L.; He, S.; Xiao, J.; Yang, Y. Inhibition of ubiquitin specific protease 1 sensitizes colorectal cancer cells to DNA-damaging chemotherapeutics. *Front. Oncol.,* **2019**, *9*, 1406.
http://dx.doi.org/10.3389/fonc.2019.01406 PMID: 31921663

[218] Dees, S.; Pontiggia, L.; Jasmin, J.F.; Mercier, I. Phosphorylated STAT3 (Tyr705) as a biomarker of response to pimozide treatment in triple-negative breast cancer. *Cancer Biol. Ther.,* **2020**, *21*(6), 506-521.
http://dx.doi.org/10.1080/15384047.2020.1726718 PMID: 32164483

[219] Strobl, J.S.; Kirkwood, K.L.; Lantz, T.K.; Lewine, M.A.; Peterson, V.A.; Worley, J.F., III Inhibition of human breast cancer cell proliferation in tissue culture by the neuroleptic agents pimozide and thioridazine. *Cancer Res.,* **1990**, *50*(17), 5399-5405.
PMID: 2386945

[220] Strobl, J.S.; Peterson, V.A. Tamoxifen-resistant human breast cancer cell growth: inhibition by thioridazine, pimozide and the calmodulin antagonist, W-13. *J. Pharmacol. Exp. Ther.,* **1992**, *263*(1), 186-193.
PMID: 1403784

[221] Strobl, J.S.; Melkoumian, Z.; Peterson, V.A.; Hylton, H. The cell death response to gamma-radiation in MCF-7 cells is enhanced by a neuroleptic drug, pimozide. *Breast Cancer Res. Treat.,* **1998**, *51*(1), 83-95.
http://dx.doi.org/10.1023/A:1006046604062 PMID: 9877031

[222] Lee, E.; Yong, R.L.; Paddison, P.; Zhu, J. Comparison of glioblastoma (GBM) molecular classification methods. *Semin. Cancer Biol.,* **2018**, *53*, 201-211.
http://dx.doi.org/10.1016/j.semcancer.2018.07.006 PMID: 30031763

[223] Elmaci, I.; Altinoz, M.A. Targeting the cellular schizophrenia. Likely employment of the antipsychotic agent pimozide in treatment of refractory cancers and glioblastoma. *Crit. Rev. Oncol. Hematol.,* **2018**, *128*, 96-109.
http://dx.doi.org/10.1016/j.critrevonc.2018.06.004 PMID: 29958636

[224] Sachdeva, R.; Wu, M.; Smiljanic, S.; Kaskun, O.; Ghannad-Zadeh, K.; Celebre, A.; Isaev, K.; Morrissy, A.S.; Guan, J.; Tong, J.; Chan, J.; Wilson, T.M.; Al-Omaishi, S.; Munoz, D.G.; Dirks, P.B.; Moran, M.F.; Taylor, M.D.; Reimand, J.; Das, S. ID1 is critical for tumorigenesis and regulates chemoresistance in glioblastoma. *Cancer Res.,* **2019**, *79*(16), 4057-4071.
http://dx.doi.org/10.1158/0008-5472.CAN-18-1357 PMID: 31292163

[225] Perk, J.; Iavarone, A.; Benezra, R. Id family of helix-loop-helix proteins in cancer. *Nat. Rev. Cancer,* **2005**, *5*(8), 603-614.
http://dx.doi.org/10.1038/nrc1673 PMID: 16034366

[226] Liang, Q.; Dexheimer, T.S.; Zhang, P.; Rosenthal, A.S.; Villamil, M.A.; You, C.; Zhang, Q.; Chen, J.; Ott, C.A.; Sun, H.; Luci, D.K.; Yuan, B.; Simeonov, A.; Jadhav, A.; Xiao, H.; Wang, Y.; Maloney, D.J.; Zhuang, Z. A selective USP1-UAF1 inhibitor links deubiquitination to DNA damage responses. *Nat. Chem. Biol.,* **2014**, *10*(4), 298-304.
http://dx.doi.org/10.1038/nchembio.1455 PMID: 24531842

[227] Zhou, W.; Chen, M.K.; Yu, H.T.; Zhong, Z.H.; Cai, N.; Chen, G.Z.; Zhang, P.; Chen, J.J. The antipsychotic drug pimozide inhibits cell growth in prostate cancer through suppression of STAT3 activation. *Int. J. Oncol.,* **2016**, *48*(1), 322-328.
http://dx.doi.org/10.3892/ijo.2015.3229 PMID: 26549437

[228] Kim, U.; Kim, C.Y.; Lee, J.M.; Ryu, B.; Kim, J.; Shin, C.; Park, J.H. Pimozide inhibits the human prostate cancer cells through the generation of reactive oxygen species. *Front. Pharmacol.,* **2020**, *10*, 1517.
http://dx.doi.org/10.3389/fphar.2019.01517 PMID: 32009948

[229] Fako, V.; Yu, Z.; Henrich, C.J.; Ransom, T.; Budhu, A.S.; Wang, X.W. Inhibition of Wnt/β-catenin signaling in hepatocellular carcinoma by an antipsychotic drug pimozide. *Int. J. Biol. Sci.,* **2016**, *12*(7), 768-775.
http://dx.doi.org/10.7150/ijbs.14718 PMID: 27313491

[230] Cai, N.; Zhou, W.; Ye, L.L.; Chen, J.; Liang, Q.N.; Chang, G.; Chen, J.J. The STAT3 inhibitor pimozide impedes cell proliferation and induces ROS generation in human osteosarcoma by suppressing catalase expression. *Am. J. Transl. Res.,* **2017**, *9*(8), 3853-3866.
PMID: 28861175

[231] Jia, H.; Ren, W.; Feng, Y.; Wei, T.; Guo, M.; Guo, J.; Zhao, J.; Song, X.; Wang, M.; Zhao, T.; Wang, H.; Feng, Z.; Tian, Z. The enhanced antitumour response of pimozide combined

with the IDO inhibitor L-MT in melanoma. *Int. J. Oncol.,* **2018**, *53*(3), 949-960. http://dx.doi.org/10.3892/ijo.2018.4473 PMID: 30015838

[232] Thanacoody, R.H. Thioridazine: the good and the bad. *Recent Pat Antiinfect Drug Discov,* **2011**, *6*(2), 92-98. http://dx.doi.org/10.2174/157489111796064588 PMID: 21548877

[233] Sultana, A.; Reilly, J.; Fenton, M. Thioridazine for schizophrenia. *Cochrane Database Syst. Rev.,* **2000**, *3*(3)CD001944 PMID: 10908517

[234] Dean, L. Thioridazine therapy and CYP2D6 genotypes.*Medical Genetics Summaries*; Pratt, V.M.; McLeod, H.L.; Rubinstein, W.S.; Scott, S.A.; Dean, L.C.; Kattman, B.L.; Malheiro, A.J., Eds.; National Center for Biotechnology Information (US): Bethesda, MD, **2012**.

[235] Serafin, M.B.; Bottega, A.; da Rosa, T.F.; Machado, C.S.; Foletto, V.S.; Coelho, S.S.; da Mota, A.D.; Hörner, R. Drug repositioning in oncology. *Am. J. Ther.,* **2019**, ••• http://dx.doi.org/10.1097/MJT.0000000000000906 PMID: 31033488

[236] Yong, M.; Yu, T.; Tian, S.; Liu, S.; Xu, J.; Hu, J.; Hu, L. DR2 blocker thioridazine: A promising drug for ovarian cancer therapy. *Oncol. Lett.,* **2017**, *14*(6), 8171-8177. http://dx.doi.org/10.3892/ol.2017.7184 PMID: 29344260

[237] Yue, H.; Huang, D.; Qin, L.; Zheng, Z.; Hua, L.; Wang, G.; Huang, J.; Huang, H. Targeting lung cancer stem cells with antipsychological drug thioridazine. *BioMed Res. Int.,* **2016**, *2016*6709828 http://dx.doi.org/10.1155/2016/6709828 PMID: 27556038

[238] Kang, S.; Dong, S.M.; Kim, B.R.; Park, M.S.; Trink, B.; Byun, H.J.; Rho, S.B. Thioridazine induces apoptosis by targeting the PI3K/Akt/mTOR pathway in cervical and endometrial cancer cells. *Apoptosis,* **2012**, *17*(9), 989-997. http://dx.doi.org/10.1007/s10495-012-0717-2 PMID: 22460505

[239] Rho, S.B.; Kim, B.R.; Kang, S. A gene signature-based approach identifies thioridazine as an inhibitor of phosphatidylinositol-3′-kinase (PI3K)/AKT pathway in ovarian cancer cells. *Gynecol. Oncol.,* **2011**, *120*(1), 121-127. http://dx.doi.org/10.1016/j.ygyno.2010.10.003 PMID: 21035837

[240] Qian, G.; Dai, L.; Yu, T. Thioridazine sensitizes cisplatin against chemoresistant human lung and ovary cancer cells. *DNA Cell Biol.,* **2019**, *38*(7), 718-724. http://dx.doi.org/10.1089/dna.2019.4715 PMID: 31188023

[241] Park, M.S.; Dong, S.M.; Kim, B.R.; Seo, S.H.; Kang, S.; Lee, E.J.; Lee, S.H.; Rho, S.B. Thioridazine inhibits angiogenesis and tumor growth by targeting the VEGFR-2/PI3K/mTOR pathway in ovarian cancer xenografts. *Oncotarget,* **2014**, *5*(13), 4929-4934. http://dx.doi.org/10.18632/oncotarget.2063 PMID: 24952635

[242] Byun, H.J.; Lee, J.H.; Kim, B.R.; Kang, S.; Dong, S.M.; Park, M.S.; Lee, S.H.; Park, S.H.; Rho, S.B. Anti-angiogenic effects of thioridazine involving the FAK-mTOR pathway. *Microvasc. Res.,* **2012**, *84*(3), 227-234. http://dx.doi.org/10.1016/j.mvr.2012.09.006 PMID: 23022044

[243] Chu, C.W.; Ko, H.J.; Chou, C.H.; Cheng, T.S.; Cheng, H.W.; Liang, Y.H.; Lai, Y.L.; Lin, C.Y.; Wang, C.; Loh, J.K.; Cheng, J.T.; Chiou, S.J.; Su, C.L.; Huang, C.F.; Hong, Y.R. Thioridazine enhances P62-mediated autophagy and apoptosis through Wnt/β-catenin signaling pathway in glioma cells. *Int. J. Mol. Sci.,* **2019**, *20*(3)E473 http://dx.doi.org/10.3390/ijms20030473 PMID: 30678307

[244] Sachlos, E.; Risueño, R.M.; Laronde, S.; Shapovalova, Z.; Lee, J.H.; Russell, J.; Malig, M.; McNicol, J.D.; Fiebig-Comyn, A.; Graham, M.; Levadoux-Martin, M.; Lee, J.B.; Giacomelli, A.O.; Hassell, J.A.; Fischer-Russell, D.; Trus, M.R.; Foley, R.; Leber, B.; Xenocostas, A.; Brown, E.D.; Collins, T.J.; Bhatia, M. Identification of drugs including a dopamine receptor antagonist that selectively target cancer stem cells. *Cell,* **2012**, *149*(6), 1284-1297. http://dx.doi.org/10.1016/j.cell.2012.03.049 PMID: 22632761

[245] Batash, R.; Asna, N.; Schaffer, P.; Francis, N.; Schaffer, M. Glioblastoma multiforme, diagnosis and treatment; Recent literature review. *Curr. Med. Chem.,* **2017**, *24*(27), 3002-3009. http://dx.doi.org/10.2174/0929867324666170516123206 PMID: 28521700

[246] Johannessen, T.C.; Hasan-Olive, M.M.; Zhu, H.; Denisova, O.; Grudic, A.; Latif, M.A.; Saed, H.; Varughese, J.K.; Røsland, G.V.; Yang, N.; Sundstrøm, T.; Nordal, A.; Tronstad, K.J.; Wang, J.; Lund-Johansen, M.; Simonsen, A.; Janji, B.; Westermarck, J.; Bjerkvig, R.; Prestegarden, L. Thioridazine inhibits autophagy and sensitizes glioblastoma cells to temozolomide. *Int. J. Cancer,* **2019**, *144*(7), 1735-1745. http://dx.doi.org/10.1002/ijc.31912 PMID: 30289977

[247] Cheng, H.W.; Liang, Y.H.; Kuo, Y.L.; Chuu, C.P.; Lin, C.Y.; Lee, M.H.; Wu, A.T.; Yeh, C.T.; Chen, E.I.; Whang-Peng, J.; Su, C.L.; Huang, C.Y. Identification of thioridazine, an antipsychotic drug, as an antiglioblastoma and anticancer stem cell agent using public gene expression data. *Cell Death Dis.,* **2015**, *6*e1753 http://dx.doi.org/10.1038/cddis.2015.77 PMID: 25950483

[248] Zhao, Y.; Bao, Q.; Renner, A.; Camaj, P.; Eichhorn, M.; Ischenko, I.; Angele, M.; Kleespies, A.; Jauch, K.W.; Bruns, C. Cancer stem cells and angiogenesis. *Int. J. Dev. Biol.,* **2011**, *55*(4-5), 477-482. http://dx.doi.org/10.1387/ijdb.103225yz PMID: 21732274

[249] Rich, J.N. Cancer stem cells in radiation resistance. *Cancer Res.,* **2007**, *67*(19), 8980-8984. http://dx.doi.org/10.1158/0008-5472.CAN-07-0895 PMID: 17908997

[250] Massard, C.; Deutsch, E.; Soria, J.C. Tumour stem cell-targeted treatment: elimination or differentiation. *Ann. Oncol.,* **2006**, *17*(11), 1620-1624. http://dx.doi.org/10.1093/annonc/mdl074 PMID: 16600978

[251] Shen, J.; Ma, B.; Zhang, X.; Sun, X.; Han, J.; Wang, Y.; Chu, L.; Xu, H.; Yang, Y. Thioridazine has potent antitumor effects on lung cancer stem-like cells. *Oncol. Lett.,* **2017**, *13*(3), 1563-1568. http://dx.doi.org/10.3892/ol.2017.5651 PMID: 28454291

[252] Torre, L.A.; Trabert, B.; DeSantis, C.E.; Miller, K.D.; Samimi, G.; Runowicz, C.D.; Gaudet, M.M.; Jemal, A.; Siegel, R.L. Ovarian cancer statistics, 2018. *CA Cancer J. Clin.,* **2018**, *68*(4), 284-296. http://dx.doi.org/10.3322/caac.21456 PMID: 29809280

[253] Liu, J.K.; Hao, Y.J.; Huang, J.W.; Li, X.; Cai, H.B.; Peng, K. [Mechanism of thioridazine-induced apoptosis of human colorectal cancer SW480 cells]. *Nan Fang Yi Ke Da Xue Xue Bao,* **2015**, *35*(4), 511-515. PMID: 25907934

[254] Mu, J.; Xu, H.; Yang, Y.; Huang, W.; Xiao, J.; Li, M.; Tan, Z.; Ding, Q.; Zhang, L.; Lu, J.; Wu, X.; Liu, Y. Thioridazine, an antipsychotic drug, elicits potent antitumor effects in gastric cancer. *Oncol. Rep.,* **2014**, *31*(5), 2107-2114. http://dx.doi.org/10.3892/or.2014.3068 PMID: 24604290

[255] Tegowski, M.; Fan, C.; Baldwin, A.S. Thioridazine inhibits self-renewal in breast cancer cells via DRD2-dependent STAT3 inhibition, but induces a G_1 arrest independent of DRD2. *J. Biol. Chem.,* **2018**, *293*(41), 15977-15990. http://dx.doi.org/10.1074/jbc.RA118.003719 PMID: 30131338

[256] Seo, S.U.; Cho, H.K.; Min, K.J.; Woo, S.M.; Kim, S.; Park, J.W.; Kim, S.H.; Choi, Y.H.; Keum, Y.S.; Hyun, J.W.; Park, H.H.; Lee, S.H.; Kim, D.E.; Kwon, T.K. Thioridazine enhances sensitivity to carboplatin in human head and neck cancer cells through downregulation of c-FLIP and Mcl-1 expression. *Cell Death Dis.,* **2017**, *8*(2)e2599 http://dx.doi.org/10.1038/cddis.2017.8 PMID: 28182008

[257] Min, K.J.; Seo, B.R.; Bae, Y.C.; Yoo, Y.H.; Kwon, T.K. Antipsychotic agent thioridazine sensitizes renal carcinoma Caki cells to TRAIL-induced apoptosis through reactive oxygen species-mediated inhibition of Akt signaling and downregulation of Mcl-1 and c-FLIP(L). *Cell Death Dis.,* **2014**, *5*e1063 http://dx.doi.org/10.1038/cddis.2014.35 PMID: 24556678

[258] Meng, Q.; Sun, X.; Wang, J.; Wang, Y. [Mechanism of thioridazine plus medroxyprogesterone in the treatment of endometrial cancer]. *Zhonghua Yi Xue Za Zhi,* **2015**, *95*(19), 1540-1543. PMID: 26178512

[259] Chen, T.; Hu, Y.; Liu, B.; Huang, X.; Li, Q.; Gao, N.; Jin, Z.; Jia, T.; Guo, D.; Jin, G. Combining thioridazine and loratadine for the treatment of gastrointestinal tumor. *Oncol. Lett.,* **2017**, *14*(4), 4573-4580. http://dx.doi.org/10.3892/ol.2017.6815 PMID: 29085455

[260] Seo, S.U.; Kim, T.H.; Kim, D.E.; Min, K.J.; Kwon, T.K. NOX4-mediated ROS production induces apoptotic cell death via down-regulation of c-FLIP and Mcl-1 expression in combined treatment with thioridazine and curcumin. *Redox Biol.,* **2017**, *13*, 608-622. http://dx.doi.org/10.1016/j.redox.2017.07.017 PMID: 28806703

[261] Ke, X.Y.; Lin Ng, V.W.; Gao, S.J.; Tong, Y.W.; Hedrick, J.L.; Yang, Y.Y. Co-delivery of thioridazine and doxorubicin using polymeric micelles for targeting both cancer cells and cancer stem cells. *Biomaterials,* **2014**, *35*(3), 1096-1108. http://dx.doi.org/10.1016/j.biomaterials.2013.10.049 PMID: 24183698

[262] Jin, X.; Zou, B.; Luo, L.; Zhong, C.; Zhang, P.; Cheng, H.; Guo, Y.; Gou, M. Codelivery of thioridazine and doxorubicin using nanoparticles for effective breast cancer therapy. *Int. J. Nanomedicine,* **2016**, *11*, 4545-4552. http://dx.doi.org/10.2147/IJN.S104635 PMID: 27660446

[263] Koch, K.; Mansi, K.; Haynes, E.; Adams, C.E.; Sampson, S.; Furtado, V.A. Trifluoperazine versus placebo for schizophrenia. *Cochrane Database Syst. Rev.,* **2014**, *1*(1)CD010226 PMID: 24414883

[264] Marques, L.O.; Lima, M.S.; Soares, B.G. Trifluoperazine for schizophrenia. *Cochrane Database Syst. Rev.,* **2004**, *1*(1)CD003545 PMID: 14974020

[265] Howland, R.H. Trifluoperazine: A sprightly old drug. *J. Psychosoc. Nurs. Ment. Health Serv.,* **2016**, *54*(1), 20-22. http://dx.doi.org/10.3928/02793695-20151223-01 PMID: 26760133

[266] Tardy, M.; Dold, M.; Engel, R.R.; Leucht, S. Trifluoperazine versus low-potency first-generation antipsychotic drugs for schizophrenia. *Cochrane Database Syst. Rev.,* **2014**, *7*(7)CD009396 http://dx.doi.org/10.1002/14651858.CD009396.pub2 PMID: 25003310

[267] Kang, S.; Hong, J.; Lee, J.M.; Moon, H.E.; Jeon, B.; Choi, J.; Yoon, N.A.; Paek, S.H.; Roh, E.J.; Lee, C.J.; Kang, S.S. Trifluoperazine, a well-known antipsychotic, inhibits glioblastoma invasion by binding to calmodulin and disinhibiting calcium release channel IP3R. *Mol. Cancer Ther.,* **2017**, *16*(1), 217-227. http://dx.doi.org/10.1158/1535-7163.MCT-16-0169-T PMID: 28062709

[268] Feng, Z.; Xia, Y.; Gao, T.; Xu, F.; Lei, Q.; Peng, C.; Yang, Y.; Xue, Q.; Hu, X.; Wang, Q.; Wang, R.; Ran, Z.; Zeng, Z.; Yang, N.; Xie, Z.; Yu, L. The antipsychotic agent trifluoperazine hydrochloride suppresses triple-negative breast cancer tumor growth and brain metastasis by inducing G0/G1 arrest and apoptosis. *Cell Death Dis.,* **2018**, *9*(10), 1006. http://dx.doi.org/10.1038/s41419-018-1046-3 PMID: 30258182

[269] Gao, Y.; Sun, T.Y.; Bai, W.F.; Bai, C.G. Design, synthesis and evaluation of novel phenothiazine derivatives as inhibitors of breast cancer stem cells. *Eur. J. Med. Chem.,* **2019**, *183*111692 http://dx.doi.org/10.1016/j.ejmech.2019.111692 PMID: 31541872

[270] Goyette, M.A.; Cusseddu, R.; Elkholi, I.; Abu-Thuraia, A.; El-Hachem, N.; Haibe-Kains, B.; Gratton, J.P.; Côté, J.F. AXL knockdown gene signature reveals a drug repurposing opportunity for a class of antipsychotics to reduce growth and metastasis of triple-negative breast cancer. *Oncotarget,* **2019**, *10*(21), 2055-2067. http://dx.doi.org/10.18632/oncotarget.26725 PMID: 31007848

[271] Pulkoski-Gross, A.; Li, J.; Zheng, C.; Li, Y.; Ouyang, N.; Rigas, B.; Zucker, S.; Cao, J. Repurposing the antipsychotic trifluoperazine as an antimetastasis agent. *Mol. Pharmacol.,* **2015**, *87*(3), 501-512. http://dx.doi.org/10.1124/mol.114.096941 PMID: 25552486

[272] Park, S.H.; Chung, Y.M.; Ma, J.; Yang, Q.; Berek, J.S.; Hu, M.C. Pharmacological activation of FOXO3 suppresses triple-negative breast cancer *in vitro* and *in vivo*. *Oncotarget,* **2016**, *7*(27), 42110-42125. http://dx.doi.org/10.18632/oncotarget.9881 PMID: 27283899

[273] O'Sullivan, C.C.; Davarpanah, N.N.; Abraham, J.; Bates, S.E. Current challenges in the management of breast cancer brain metastases. *Semin. Oncol.,* **2017**, *44*(2), 85-100. http://dx.doi.org/10.1053/j.seminoncol.2017.06.006 PMID: 28923217

[274] Pinheiro, T.; Otrocka, M.; Seashore-Ludlow, B.; Rraklli, V.; Holmberg, J.; Forsberg-Nilsson, K.; Simon, A.; Kirkham, M. A chemical screen identifies trifluoperazine as an inhibitor of glioblastoma growth. *Biochem. Biophys. Res. Commun.,* **2017**, *494*(3-4), 477-483. http://dx.doi.org/10.1016/j.bbrc.2017.10.106 PMID: 29066348

[275] Zhang, X.; Xu, R.; Zhang, C.; Xu, Y.; Han, M.; Huang, B.; Chen, A.; Qiu, C.; Thorsen, F.; Prestegarden, L.; Bjerkvig, R.; Wang, J.; Li, X. Trifluoperazine, a novel autophagy inhibitor, increases radiosensitivity in glioblastoma by impairing homologous recombination. *J. Exp. Clin. Cancer Res.,* **2017**, *36*(1), 118. http://dx.doi.org/10.1186/s13046-017-0588-z PMID: 28870216

[276] Wen, Y.; Zhang, Y.; Li, J.; Luo, F.; Huang, Z.; Liu, K. Low concentration trifluoperazine promotes proliferation and re-

duces calcium-dependent apoptosis in glioma cells. *Sci. Rep.,* **2018**, *8*(1), 1147. http://dx.doi.org/10.1038/s41598-018-19413-y PMID: 29348654

[277] Qian, K.; Sun, L.; Zhou, G.; Ge, H.; Meng, Y.; Li, J.; Li, X.; Fang, X. Trifluoperazine as an alternative strategy for the inhibition of tumor growth of colorectal cancer. *J. Cell. Biochem.,* **2019**, *120*(9), 15756-15765. http://dx.doi.org/10.1002/jcb.28845 PMID: 31081173

[278] Jiang, J.; Huang, Z.; Chen, X.; Luo, R.; Cai, H.; Wang, H.; Zhang, H.; Sun, T.; Zhang, Y. Trifluoperazine activates FOXO1-related signals to inhibit tumor growth in hepatocellular carcinoma. *DNA Cell Biol.,* **2017**, *36*(10), 813-821. http://dx.doi.org/10.1089/dna.2017.3790 PMID: 28876084

[279] Yeh, C.T.; Wu, A.T.; Chang, P.M.; Chen, K.Y.; Yang, C.N.; Yang, S.C.; Ho, C.C.; Chen, C.C.; Kuo, Y.L.; Lee, P.Y.; Liu, Y.W.; Yen, C.C.; Hsiao, M.; Lu, P.J.; Lai, J.M.; Wang, L.S.; Wu, C.H.; Chiou, J.F.; Yang, P.C.; Huang, C.Y. Trifluoperazine, an antipsychotic agent, inhibits cancer stem cell growth and overcomes drug resistance of lung cancer. *Am. J. Respir. Crit. Care Med.,* **2012**, *186*(11), 1180-1188. http://dx.doi.org/10.1164/rccm.201207-1180OC PMID: 23024022

[280] Chen, Q.Y.; Wu, L.J.; Wu, Y.Q.; Lu, G.H.; Jiang, Z.Y.; Zhan, J.W.; Jie, Y.; Zhou, J.Y. Molecular mechanism of trifluoperazine induces apoptosis in human A549 lung adenocarcinoma cell lines. *Mol. Med. Rep.,* **2009**, *2*(5), 811-817. http://dx.doi.org/10.3892/mmr_00000177 PMID: 21475906

[281] Polischouk, A.G.; Holgersson, A.; Zong, D.; Stenerlöw, B.; Karlsson, H.L.; Möller, L.; Viktorsson, K.; Lewensohn, R. The antipsychotic drug trifluoperazine inhibits DNA repair and sensitizes non small cell lung carcinoma cells to DNA double-strand break induced cell death. *Mol. Cancer Ther.,* **2007**, *6*(8), 2303-2309. http://dx.doi.org/10.1158/1535-7163.MCT-06-0402 PMID: 17699725

[282] Perez, R.P.; Handel, L.M.; Hamilton, T.C. Potentiation of cisplatin cytotoxicity in human ovarian carcinoma cell lines by trifluoperazine, a calmodulin inhibitor. *Gynecol. Oncol.,* **1992**, *46*(1), 82-87. http://dx.doi.org/10.1016/0090-8258(92)90201-S PMID: 1634144

[283] Naftalovich, S.; Yefenof, E.; Eilam, Y. Antitumor effects of ketoconazole and trifluoperazine in murine T-cell lymphomas. *Cancer Chemother. Pharmacol.,* **1991**, *28*(5), 384-390. http://dx.doi.org/10.1007/BF00685694 PMID: 1914083

[284] Kamath, N.; Grabowski, D.; Ford, J.; Ganapathi, R. Calmodulin inhibitor trifluoperazine in combination with doxorubicin induces the selection of tumour cells with the multidrug resistant phenotype. *Br. J. Cancer,* **1993**, *67*(6), 1203-1208. http://dx.doi.org/10.1038/bjc.1993.226 PMID: 8099806

[285] Abad, A.; Masuti, B.; Camps, C.; Font, A.; Balañá, C.; Vicent, J.M.; Sánchez, J.J. Epirubicin plus a calmodulin inhibitor (trifluoperazine) activity in advanced pancreatic adenocarcinoma. *Eur. J. Cancer,* **1994**, *30A*(7), 1043. http://dx.doi.org/10.1016/0959-8049(94)90155-4 PMID: 7946573

[286] Mørch, L.S.; Dehlendorff, C.; Baandrup, L.; Friis, S.; Kjaer, S.K. Use of antidepressants and risk of epithelial ovarian cancer. *Int. J. Cancer,* **2017**, *141*(11), 2197-2203. http://dx.doi.org/10.1002/ijc.30919 PMID: 28791695

[287] Rahman, T.; Clevenger, C.V.; Kaklamani, V.; Lauriello, J.; Campbell, A.; Malwitz, K.; Kirkland, R.S. Antipsychotic treatment in breast cancer patients. *Am. J. Psychiatry,* **2014**, *171*(6), 616-621. http://dx.doi.org/10.1176/appi.ajp.2013.13050650 PMID: 24880509

[288] Tworoger, S.S.; Hankinson, S.E. Prolactin and breast cancer risk. *Cancer Lett.,* **2006**, *243*(2), 160-169. http://dx.doi.org/10.1016/j.canlet.2006.01.032 PMID: 16530327

[289] Fond, G.; Macgregor, A.; Attal, J.; Larue, A.; Brittner, M.; Ducasse, D.; Capdevielle, D. Antipsychotic drugs: pro-cancer or anti-cancer? A systematic review. *Med. Hypotheses,* **2012**, *79*(1), 38-42. http://dx.doi.org/10.1016/j.mehy.2012.03.026 PMID: 22543071

[290] Rajagopal, S. Clozapine, agranulocytosis, and benign ethnic neutropenia. *Postgrad. Med. J.,* **2005**, *81*(959), 545-546. http://dx.doi.org/10.1136/pgmj.2004.031161 PMID: 16143678

[291] Nielsen, J.; Boysen, A. Clozapine treatment associated with increased risk of acute myeloid leukemia (AML). *Schizophr. Res.,* **2010**, *123*(2-3), 270-272. http://dx.doi.org/10.1016/j.schres.2010.08.035 PMID: 20850952

[292] Miguel, C.; Albuquerque, E. Drug interaction in psycho-oncology: antidepressants and antineoplastics. *Pharmacology,* **2011**, *88*(5-6), 333-339. http://dx.doi.org/10.1159/000334738 PMID: 22123153

[293] Kalash, G.R. Psychotropic drug metabolism in the cancer patient: clinical aspects of management of potential drug interactions. *Psychooncology,* **1998**, *7*(4), 307-320. http://dx.doi.org/10.1002/(SICI)1099-1611(199807/08)7:4<307::AID-PON366>3.0.CO;2-3 PMID: 9741070

[294] Ciraulo, D.A.; Shader, R.I.; Greenblatt, D.J.; Creelman, W.L. *Drug Interactions in Psychiatry,* 3rd ed; Lippincott Williams & Wilkins: Philadelphia, **2006**.

[295] Kelly, C.M.; Juurlink, D.N.; Gomes, T.; Duong-Hua, M.; Pritchard, K.I.; Austin, P.C.; Paszat, L.F. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: A population based cohort study. *BMJ,* **2010**, *340*, c693.81. http://dx.doi.org/10.1136/bmj.c693

[296] Chubak, J.; Bowles, E.J.; Yu, O.; Buist, D.S.; Fujii, M.; Boudreau, D.M. Breast cancer recurrence in relation to antidepressant use. *Cancer Causes Control,* **2016**, *27*(1), 125-136. http://dx.doi.org/10.1007/s10552-015-0689-y PMID: 26518198

[297] Damodaran, S.E.; Pradhan, S.C.; Umamaheswaran, G.; Kadambari, D.; Reddy, K.S.; Adithan, C. Genetic polymorphisms of CYP2D6 increase the risk for recurrence of breast cancer in patients receiving tamoxifen as an adjuvant therapy. *Cancer Chemother. Pharmacol.,* **2012**, *70*(1), 75-81. http://dx.doi.org/10.1007/s00280-012-1891-1 PMID: 22623212

[298] Valachis, A.; Garmo, H.; Weinman, J.; Fredriksson, I.; Ahlgren, J.; Sund, M.; Holmberg, L. Effect of selective serotonin reuptake inhibitors use on endocrine therapy adherence and breast cancer mortality: a population-based study. *Breast Cancer Res. Treat.,* **2016**, *159*(2), 293-303. http://dx.doi.org/10.1007/s10549-016-3928-3 PMID: 27492739

[299] Haque, R.; Shi, J.; Schottinger, J.E.; Ahmed, S.A.; Cheetham, T.C.; Chung, J.; Avila, C.; Kleinman, K.; Habel, L.A.; Fletcher, S.W.; Kwan, M.L. Tamoxifen and antide-

pressant drug interaction in a cohort of 16,887 breast cancer survivors. *J. Natl. Cancer Inst.,* **2015**, *108*(3)djv337 http://dx.doi.org/10.1093/jnci/djv337 PMID: 26631176

[300] Grond, S.; Sablotzki, A. Clinical pharmacology of tramadol. *Clin. Pharmacokinet.,* **2004**, *43*(13), 879-923. http://dx.doi.org/10.2165/00003088-200443130-00004 PMID: 15509185

[301] Yap, K.Y.; Ho, Y.X.; Chui, W.K.; Chan, A. Harnessing the internet cloud for managing drug interactions with chemotherapy regimens in patients with cancer suffering from depression. *Acta Oncol.,* **2010**, *49*(8), 1235-1245. http://dx.doi.org/10.3109/02841861003801130 PMID: 20515422

[302] Tomita, T.; Yasui-Furukori, N.; Nakagami, T.; Tsuchimine, S.; Ishioka, M.; Kaneda, A.; Nakamura, K.; Kaneko, S. Therapeutic reference range for plasma concentrations of paroxetine in patients with major depressive disorders. *Ther. Drug Monit.,* **2014**, *36*(4), 480-485. http://dx.doi.org/10.1097/FTD.0000000000000036 PMID: 25014076

[303] Voican, C.S.; Corruble, E.; Naveau, S.; Perlemuter, G. Antidepressant-induced liver injury: a review for clinicians. *Am. J. Psychiatry,* **2014**, *171*(4), 404-415. http://dx.doi.org/10.1176/appi.ajp.2013.13050709 PMID: 24362450

[304] McIntyre, R.S.; Panjwani, Z.D.; Nguyen, H.T.; Woldeyohannes, H.O.; Alsuwaidan, M.; Soczynska, J.K.; Lourenco, M.T.; Konarski, J.Z.; Kennedy, S.H. The hepatic safety profile of duloxetine: a review. *Expert Opin. Drug Metab. Toxicol.,* **2008**, *4*(3), 281-285. http://dx.doi.org/10.1517/17425255.4.3.281 PMID: 18363543

[305] Leucht, S.; Corves, C.; Arbter, D.; Engel, R.R.; Li, C.; Davis, J.M. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet,* **2009**, *373*(9657), 31-41. http://dx.doi.org/10.1016/S0140-6736(08)61764-X PMID: 19058842

[306] Leucht, S.; Cipriani, A.; Spineli, L.; Mavridis, D.; Orey, D.; Richter, F.; Samara, M.; Barbui, C.; Engel, R.R.; Geddes, J.R.; Kissling, W.; Stapf, M.P.; Lässig, B.; Salanti, G.; Davis, J.M. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet,* **2013**, *382*(9896), 951-962. http://dx.doi.org/10.1016/S0140-6736(13)60733-3 PMID: 23810019

[307] Aslostovar, L.; Boyd, A.L.; Almakadi, M.; Collins, T.J.; Leong, D.P.; Tirona, R.G.; Kim, R.B.; Julian, J.A.; Xenocostas, A.; Leber, B.; Levine, M.N.; Foley, R.; Bhatia, M. A phase 1 trial evaluating thioridazine in combination with cytarabine in patients with acute myeloid leukemia. *Blood Adv.,* **2018**, *2*(15), 1935-1945. http://dx.doi.org/10.1182/bloodadvances.2018015677 PMID: 30093531

DISCLAIMER: The above article has been published in Epub (ahead of print) on the basis of the materials provided by the author. The Editorial Department reserves the right to make minor modifications for further improvement of the manuscript.